AN ENANTIO- AND DIASTEREO-SELECTIVE TOTAL SYNTHESIS OF HERBOXIDIENE METHYL ESTER

A thesis submitted for the degree of Doctor of Philosophy

of the Australian National University

by

Rajaratnam Premraj

Research School of Chemistry
Canberra, Australia

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Corrigendum

Page iii, Last line:	.....synthesis of the natural product;
Page vi:	insert Ipc = isopinocampheyl;
Page viii:	Tf = trifluoromethanesulfonyl
Pages 6, 8, 9 and 73:	(i) the illustrated stereochemistries at C15 in compounds **2**, **4**, **6**, **9** and **12** should be reversed; (ii) the stereochemistry at C14 in compounds **6, 12, 158** and **160** should also be reversed;
Pages 8 and 10:	the bond between the carbonyl carbon and ether oxygen within compound **10** should be represented by a solid line;
Page 14, Scheme 1.5:	in the caption replace (-)-IpC_2BCl with (-)-Ipc$_2$BCl;
Page 18, Line 3:	replace the phrase Under....underwent a... with After PMB protection of enol carbamate **47**, base treatment led to a ....;
Page 18, Line 12 up:	....trisubstituted alkene **59**.;
Page 19, Scheme 1.8:	(i) delete "I" from structure **56**; (ii) replace the OH group in structures **53**, **57** and **58** with OMe; (iii) compound **40** is prepared by LDA-promoted deprotonation of the corresponding protonated sulfone in THF at –80 °C;
Page 21, Line 14:	note that PMB protection was performed after the hydrolysis/cyclisation step.
Page 23, Line 10 up:	....led to the....;
Page 24, Scheme:	PCBOH = *p*-chlorobenzoic acid (a.k.a. *p*-CBA);
Page 27:	structure **88** is missing a second sulfur atom in what should be a 1,3-dithiane ring;
Page 28, Line 13:	"....and acetic acid substituents attached in a *cis* fashion."
Page 35, Line 3:	(i) omit ....the....; (ii) in structure **39** the stereochemistry of the OH group at C-18 is actually opposite to that drawn;
Page 38, Fig 2.1:	(i) in the caption replace Nmenonic with Mnemonic; (ii) a similar replacement is required at Line 3 up on Page 40;
Page 58:	the structure of compound **136** is given in Page 61;
Page 66, Line 3 up:	....(see Figure 3.10)[51,52]....(ie. insert reference numbers);
Page 69, Fig. 3.11:	a partial double bond should be inserted between C-13 and C-14 in the illustrated transition state structure;
Page 70, Line 10:	replace downfield with upfield;
Page 76, Last line:	fluoride
Page 77, Scheme 4.1:	delete the reagents for step i written to the rhs of vertical arrow;
Page 85, Fig. 4.4:	caption referring to stereochemistry at C-12 should be replaced by "this stereochemistry established by serendipitous epimerisation in a Horner-Wittig coupling step";
Page 92:	reagent under arrow near top of page should read diethyl (-)-tartrate;
Page 107, Line 3:	....hydroxylamine....;
Page 139:	Reference 47 should be I. Ohtani, T. Kusumi, Y. Kashman and H. Kakisawa, *J. Am. Chem. Soc.*, 1991, **113**, 4092.

Declaration

I declare that the material presented in this thesis represents the result of original work carried out by me during the period 1997-2000 and has not been presented for examination for any other degree. This thesis is less than 100,000 words in length. Established methodologies have been acknowledged and, wherever possible, by citation of the original publications from which they derive.

R. Premraj

Rajaratnam Premraj

29th September, 2000

Acknowledgments

I would like to thank my supervisor, Professor Martin Banwell, for his keen interest, valued discussions and enthusiasm for the work presented in this thesis. I am extremely grateful for his having given me the great opportunity in my life to join and learn from his expert research team in the area of organic synthesis.

As this project was carried out in collaboration with Dunlena Pty Ltd and CSIRO Molecular Science (Clayton), I would also like to express my sincere gratitude to Dr Greg Simpson, without whose support the PhD project would not have been.

Thank you to all the members of the Banwell group, both past and present, who have made my time in the group a happy experience. I would like to thank Dr Malcolm McLeod for giving up his time to discuss new ideas.

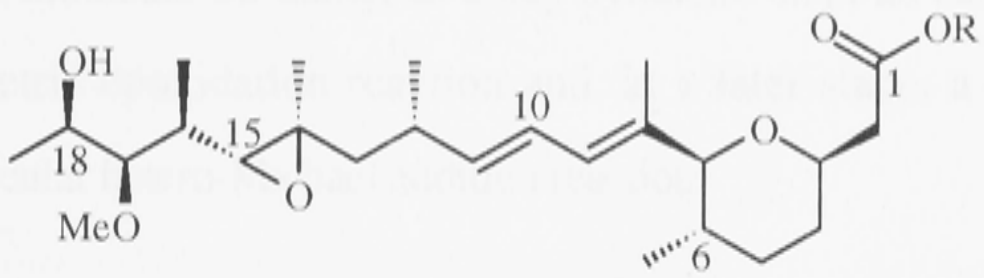
For technical support, I am indebted to Tony Herlt (HPLC) and Tin Culnane (NMR). Their expertise was invaluable and helped to make things run a lot more smoothly than might have otherwise been the case.

I am also indebted to Dr Michael Nairn for his efforts in helping to proofread this thesis.

Last, but not least, I would like to thank my family, especially my parents, brother, sisters and my wife for their never ending encouragement, support and patience.

Abstract

Herboxidiene (a.k.a. TAN-1609, **1**) is a secondary metabolite produced by, *inter alia*, *Streptomyces* species A7847. The compound was so named because it displays exceptional phytotoxicity towards a wide range of broadleaf annual weeds such as oilseed rape, wild buck wheat, morning glory and hemp sesbania while being harmless to wheat. Structurally speaking, herboxidiene is unlike any previously known phytotoxic compound and, as such, must be considered an important lead for the development of herbicides with new modes of action.



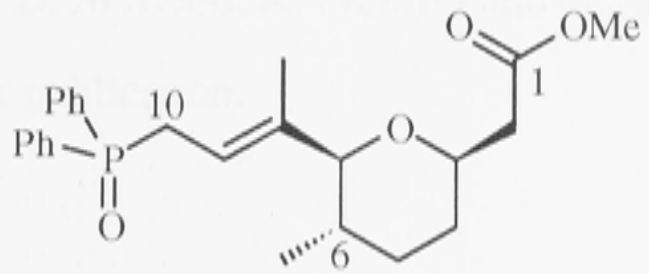
1 (R=H)
5 (R=Me)

Recently, a group of Japanese researchers revealed that herboxidiene blocks the cell-cycle at the G2 phase in human and murine tumour cells by inducing apoptosis while another group from the same country have reported that the compound up-regulates the gene expression of low-density lipoprotein receptors. On this basis, herboxidiene is of some interest as a lead compound for the development of novel agents that could be used in the treatment of certain tumours as well as excess levels of cholesterol in blood plasma.

On the basis of the foregoing, herboxidiene must be regarded as a very important synthetic target. The work described in this thesis is concerned with the development of an enantio-and diastereo-selective total synthesis of herboxidiene (**1**). This objective has been achieved by virtue of having prepared herboxidiene methyl ester (**5**), the acquisition of which constitutes a formal total synthesis of natural product.

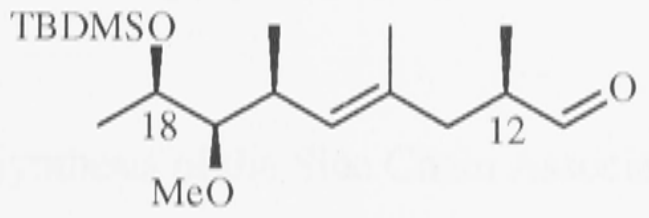
The thesis begins (Chapter One) with a commentary on the discovery and biological properties of herboxidiene (**1**). This is followed by brief descriptions of (i) degradation and synthetic studies leading to the determination of the structure of herboxidiene, (ii) the synthesis of aromatic hybrids of herboxidiene, (iii) the synthesis, by others, of a diastereoisomer of herboxidiene known as herboxidiene A, (iv) recent work, again by others, on the total synthesis of herboxidiene and, finally, (v) the retrosynthetic analysis employed by a previous member of the Banwell group and his attempts at implementation.

Chapter Two details the highly enantio- and diastereo-selective synthesis of the herboxidiene core molecule **95** using, as a key synthetic step, an early stage Katsuki-Sharpless asymmetric epoxidation reaction and, at a later stage, a highly diastereo-selective intramolecular hetero-Michael addition reaction.



95

Chapter Three describes the enantio- and diastereo-selective synthesis of the C-12 epimer of the herboxidiene side chain molecule **94** by a pathway involving, *inter alia*, an Ireland-Claisen rearrangement reaction.



12-*epi*-**94**

Chapter Four details the union of core molecule **95** and side chain aldehyde 12-*epi*-**94** using a Horner-Wittig reaction. Regio- and diastereo-controlled epoxidation of one of the resulting trienes then afforded herboxidiene methyl ester (**5**), the acquisition of which constitutes a formal total synthesis of herboxidiene itself.

Publications and Presentations Based Upon Work Carried Out During the Period of PhD Candidature

Publications:[*]

(1) The Total Synthesis of Herboxidiene, a Complex Polyketide from *Streptomyces* Species A7847.

M. G. Banwell, M. D. McLeod, R. Premraj and G. W. Simpson, *Pure Appl. Chem.*, in the press.

(2) Improved Synthetic Route to Enantiomerically Pure Samples of the Tetrahydropyranylacetic Acid Core Associated with the Phytotoxic Polyketide Herboxidiene.

M. G. Banwell, M. D. McLeod, R. Premraj and G. W. Simpson, *Aust. J. Chem.*, accepted for publication.

Presentations:

(1) The Total Synthesis of Herboxidiene, a Complex Polyketide from *Streptomyces* Species A7847.

Oral Presentation given at the Royal Australian Chemical Institute NSW Organic Group, 20th Annual One Day Symposium, 30th November, 1999.

(2) Approaches to the Synthesis of the Side Chain Associated with Herboxidiene.

Oral Presentation given at the Royal Australian Chemical Institute NSW Organic Group, 19th Annual One Day Symposium, 1st December, 1998.

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* Copies of these publications are provided in Appendix 2 at the rear of this thesis.

Glossary

The following abbreviations have been used throughout this thesis:

Ac	acetyl
a.k.a.	also known as
All	allyl
app.	apparent
APT	attached proton test
aq.	aqueous
atm.	atmosphere
Bn	benzyl
BT	benzothiazol-2-yl
Bu	butyl
Bu^t	*tert*-butyl
c	concentration (g/100 mL)
ca.	*circa* (approximately)
cat.	catalyst
CI	chemical ionisation
conc.	concentrated
δ	chemical shift (parts per million)
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DEAD	diethyl azodicarboxylate
DIAD	diisopropyl azodicarboxylate
DIBAL	diisobutylaluminium hydride
DMAD	dimethyl acetylenedicarboxylate
DMAP	4-(*N*,*N*-dimethylamino)pyridine
DME	1,2-dimethoxyethane

DMF	*N*,*N*-dimethylformamide
DMP	Dess-Martin periodinane
DMPU	*N*,*N*′-dimethylpropyleneurea
DMS	dimethyl sulfide
DMSO	dimethyl sulfoxide
dr	diastereomeric ratio
ee	enantiomeric excess
EI	electron impact
epi-	epimer
Et	ethyl
etc.	*et cetera* (and so on)
$(EtCO)_2O$	propionic anhydride
eV	electron volt
$\{^1H\}^{13}C$ NMR	fully proton decoupled ^{13}C nuclear magnetic resonance
h	hour(s)
HMPA	hexamethylphosphoramide
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrum
Hz	hertz
IR	infrared
i-Pr	*iso*-propyl
J	coupling constant (Hz)
KHMDS	potassium hexamethyldisilazide
KSAE	Katsuki-Sharpless asymmetric epoxidation
K-Selectride®	potassium tri-*sec*-butylborohydride
LDA	lithium diisopropylamide
lit.	literature
m-CPBA	*m*-chloroperbenzoic acid
$M^{+\cdot}$	molecular ion (mass spectra)

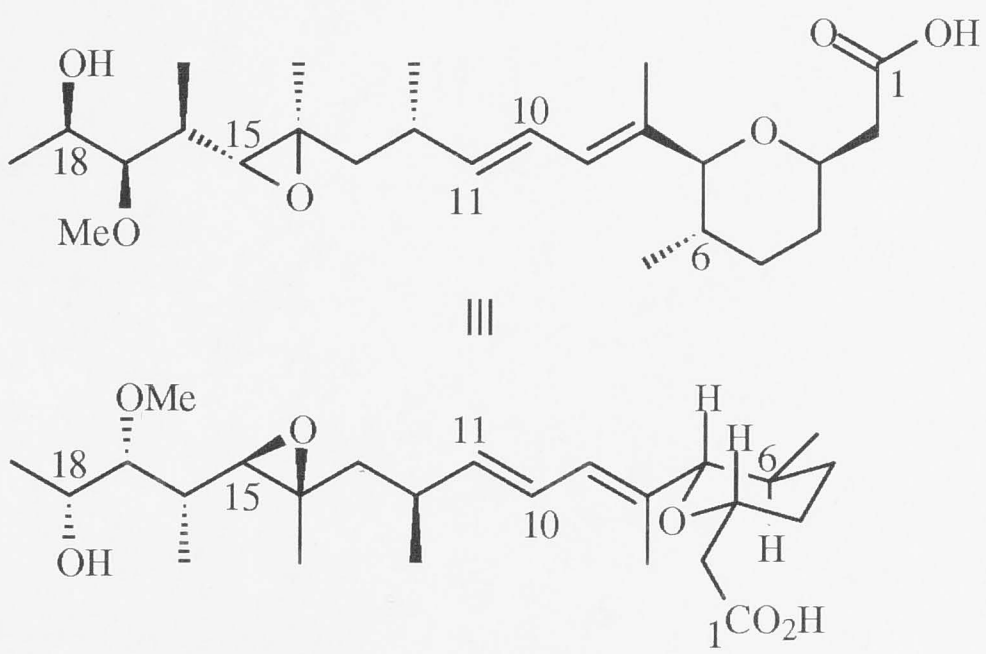
Me	methyl
m.p.	melting point (°C)
MS	mass spectrum
MTBE	methyl *tert*-butyl ether
MTPA	α-methoxy-α-trifluoromethylphenylacetic acid
m/z	mass-to-charge ratio
NMO	*N*-methylmorpholine *N*-oxide
NMR	nuclear magnetic resonance
ν_{max}	infrared absorption maximum
ORTEP	Oak Ridge Thermal Ellipsoid plot
p-CBA	*p*-chlorobenzoic acid
PCC	pyridinium chlorochromate
Ph	phenyl
PMB	*p*-methoxybenzyl
pyr	pyridine
R_f	retardation factor
R_t	retention time
rt	room temperature
TBAF	tetrabutylammonium fluoride
TBAI	tetrabutylammonium iodide
TBS or TBDMS	*tert*-butyldimethylsilyl
TBDMSCl	*tert*-butyldimethylsilyl chloride
TBDPSCl	*tert*-butyldiphenylsilyl chloride
TBME	*tert*-butylmethyl ether
TESCl	triethylsilyl chloride
TFA	trifluoroacetic acid
Tf	trifluoromethane sulfonyl
THF	tetrahydrofuran
THP	tetrahydropyran

TLC	thin layer chromatography
TMSCl	trimethylsilyl chloride
p-Ts	*para*-toluenesulfonyl or tosyl
UV	ultraviolet
V	Volts
viz.	*videlicet* (namely)
$VO(acac)_2$	oxyvanadium (IV) bis-(acetylacetonate)
<	less than
>	greater than
WHE	Wadsworth-Horner-Emmons

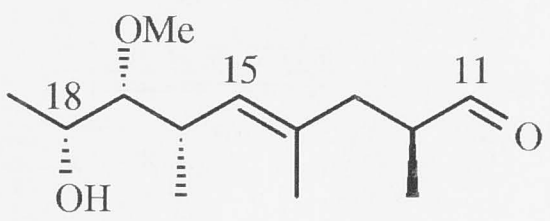
TABLE OF CONTENTS

Different Representations of Herboxidiene and Certain Sub-structures

Throughout this thesis several different representations, as shown below, have been used to illustrate the structure of herboxidiene and various key sub-structures. These varying representations reflect the different ways in which such compounds have been portrayed in the literature.



Herboxidiene (**1**)



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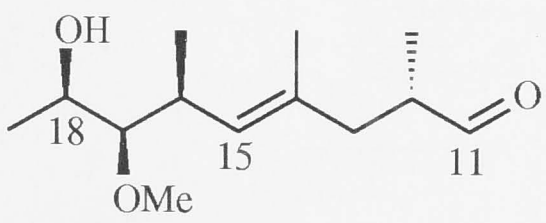
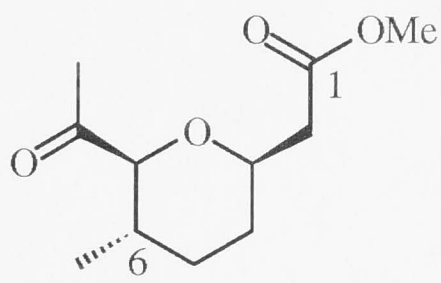


Herboxidiene Side Chain **94**



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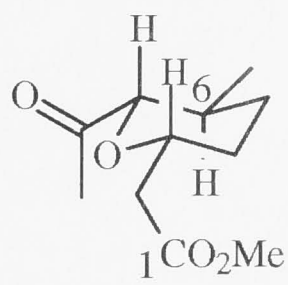


Herboxidiene Core **13**

CHAPTER ONE

Introduction

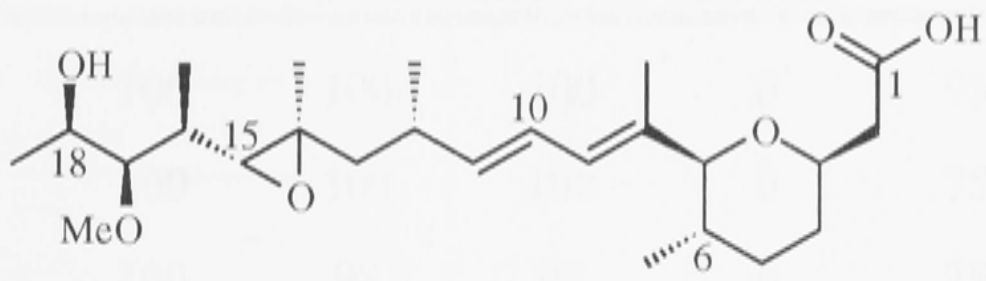
1.1 Discovery of Herboxidiene and its Biological Activities

Micro-organisms have demonstrated a remarkable ability to produce structurally diverse secondary metabolites that are toxic to plants (*viz.* the metabolites are phytotoxic). Such compounds offer the potential for controlling noxious weeds either directly or, indirectly, by providing chemists with new structural models for analogue synthesis. Examples of microbial metabolites which have been found to be toxic to plants are shown in Table 1.1[1a] and listed by "phenotype".

Table 1.1: Examples of Microbial Metabolites Known to be Phytotoxic
(Classified by Structure and/or Biosynthetic Origin)

Shikimate	**Terpenoid**	**Polyketide**	**Nucleoside**
Anisomycin	Fusicoccin	Borrelidin	Blasticidin S
Chloramphenicol	Helvolic acid	Filipin	5'-Deoxyguanosine
Cinnamic acid	Ophiobolin A	Herbimycin	Fomycins A & B
		Herboxidiene	Herbicidins A & B
		Nigericin	
		Trichothecins	
		PM-Toxin B	
Peptide	**Aminoglycoside**	**Aminoacid**	**Sugar derivative**
AM-Toxins	Kanamycin	Hadacidin	Hydantocidin
Bialaphos	Neomycin	Homoalanosine	
Phosalacine	Streptomycin	Oxetin	
Tentoxin		Phosphinothricin	
		Tabtoxinine β–lactam	
	Glutarimide	**Alkaloid**	
	Cycloheximide	Fusaric acid	
		Victoxinine	

Screening of compounds produced by microbial fermentation provides one method for uncovering novel herbicides and this approach led a group at Monsanto[1] to isolate and characterise herboxidiene (**1**), a secondary metabolite produced by *Streptomyces* sp. A7847.



1

This polyketide displays exceptional phytotoxicity towards a wide range of broadleaf annual weeds such as oilseed rape (*Brassica napus*), wild buck wheat (*Polygonum convolvulus*), morning glory (*Ipomoea* sp.) and hemp sesbania (*Sesbania exaltata*) (Table 1.2).[1] Furthermore, even at high dosage levels (5.6 kg per hectare), it is harmless to wheat (*Triticum aestivum*).

The phytotoxic properties displayed by herboxidiene are of considerable interest to Australian agriculture because this country is one of the world's leading producers of wheat. Another attraction of herboxidiene as a potential herbicide is that it is likely to be an environmentally friendly one on the expectation that it can be easily decomposed within the biosphere.

Table 1.2: Phytotoxicity of Herboxidiene (**1**)

Application Rate (kg/ha)	Soy bean	Rape	Wild Buck wheat	Morning glory	Wheat	Rice	Maize
	(% Inhibition of Growth)						
5.592	100	100	100	100	0	95	100
1.118	75	100	100	100	0	75	100
0.279	60	100	98	99	0	25	100
0.069	20	98	98	99	0	10	90
0.017	10	75	75	20	0	10	50

Note: % inhibition studies were performed using a Plant Green House Assay. Seeds of maize, rice, soybean, annual morning glory, wheat, oil seed rape, wild buckwheat and hemp sesbania were placed in furrows and covered with soil in aluminium pans. When plants reached the 1 to 3 true leaf growth stage, known amounts of herboxidiene (dissolved in acetone) were applied to the foliage at the rates indicated. The pans were placed in a green house and maintained at day/night temperatures of 30/21 °C. At 27 to 30 days after treatment, all pans were rated visually against an untreated control with 0 to 100% representing no injury and complete plant death, respectively.

Subsequent to the original report[1] that herboxidiene is a potent phytotoxic agent, a group of Japanese researchers revealed that it also has the potential to lower the risk of coronary heart disease because of its capacity to regulate the level of cholesterol in blood plasma.[2] In addition, the compound reportedly displays significant anti-tumour activity[3,4] which derives from its capacity to block the cell cycle at the G2 phase of human and murine tumour cells[3] by inducing apoptosis. The impressive IC_{50} values of herboxidiene against different lines of murine and human tumour cells are shown in Table 1.3.

Table 1.3: The IC_{50} Values of Herboxidiene (**1**) Against Various Murine and Human Tumour Cell Lines.

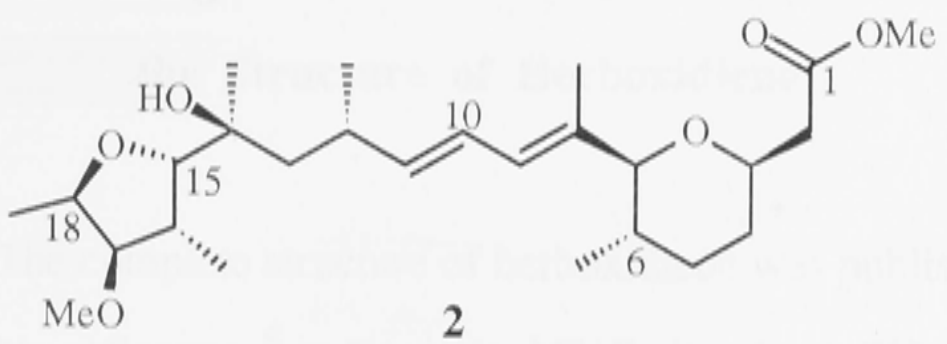
Cell-Line	IC_{50} (ng/ml)
Murine	
P815 mastocytoma	1.64
Murine EL4 lymphoma	0.79
Murine B16 melanoma	1.21
Human	
Epithelioid carcinoma	2.55
WiDr colon adenocarcinoma	12.2
SW48 colon adenocarcinoma	2.83
A549 lung carcinoma	13.7
G361 melanoma	13.3

On this basis, herboxidiene is of some interest as a lead for the development of new agents that could be used in the treatment of certain tumours as well as excess levels of cholesterol in blood plasma.

The diverse range of biological properties of herboxidiene, as delineated above, are remarkable for a linear polyketide. This situation prompted efforts by Edmunds' group at Novartis-AG (Switzerland) to determine the absolute configuration of herboxidiene[5] through a series of studies involving selective degradation of the natural product, asymmetric synthesis of the appropriate fragments and an X-ray analysis of herboxidiene itself (see Section 1.2 for details).

Structurally speaking,[5] herboxidiene is unlike any previously known phytotoxic compound and, as such, it must be considered an important lead for the development of herbicides with new modes of action. As a result, significant effort has been made to develop a comprehensive structure-activity relationship (SAR) for this compound. Much of this type of work has been undertaken by the Novartis-AG group. For example, they demonstrated that irradiation of herboxidiene leads to loss of activity (because the

compound is photolabile) as does hydrogenation of the diene moiety. Further, considerable reduction in biological activity is observed when epoxide ring opening occurs *via* intramolecular attack by the 18-hydroxyl group (thereby producing tetrahydrofuran **2**; see Figure 1.1), while if macrolactonisation occurs by attack of the 18-hydroxyl group at C-1 then the resulting compound **3** is completely inactive. Further, compound **4**, which is obtained as one of the products of the reaction of herboxidiene with anhydrous acid, does not show any useful biological activity. Interestingly, herbicidal activity is not lost when the 18-hydroxyl group is converted into an acetate, probably because the acetate cannot cyclise onto the epoxide moiety, the presence of which seems essential for activity. Perhaps even more significantly, herboxidiene methyl ester (**5**) is actually more active, as a herbicide at least, than the parent compound **1**.[6] Such SAR results are summarised in Figure 1.2.



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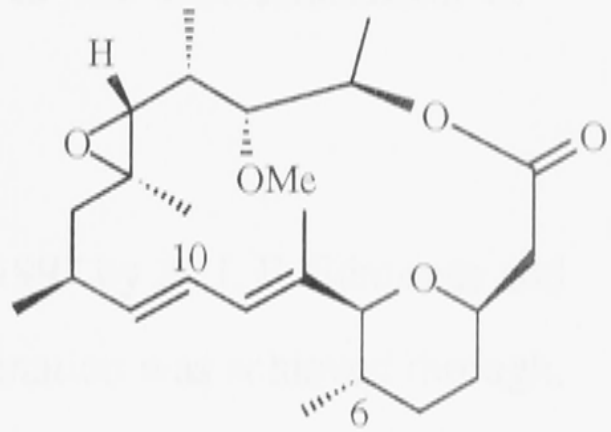

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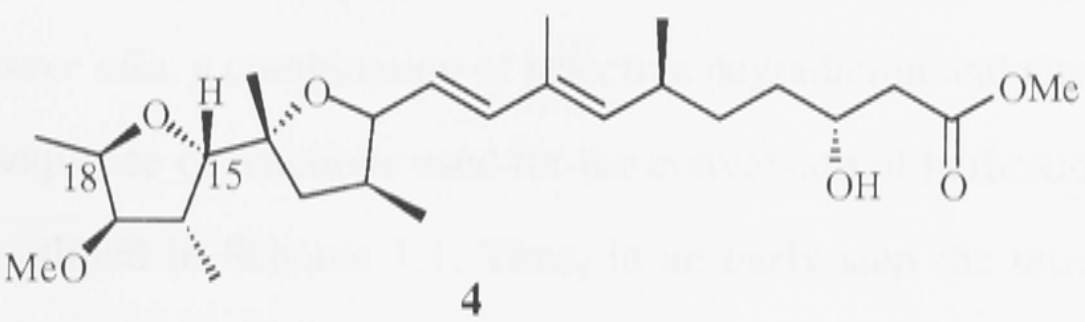

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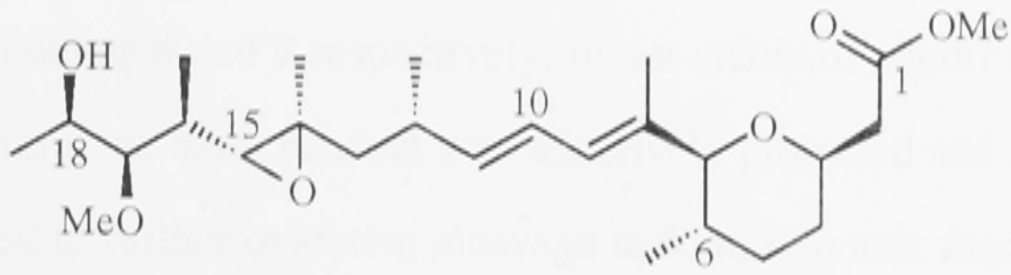
Figure 1.1: Derivatives of Herboxidiene which are Biologically Inactive.



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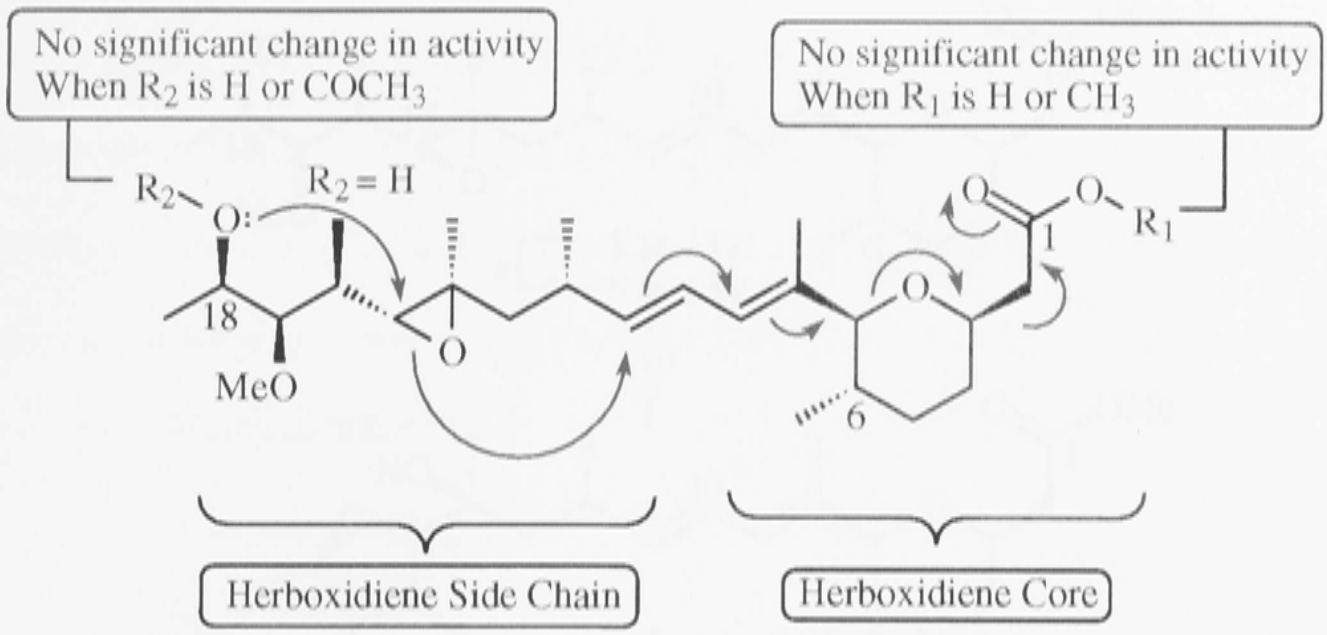
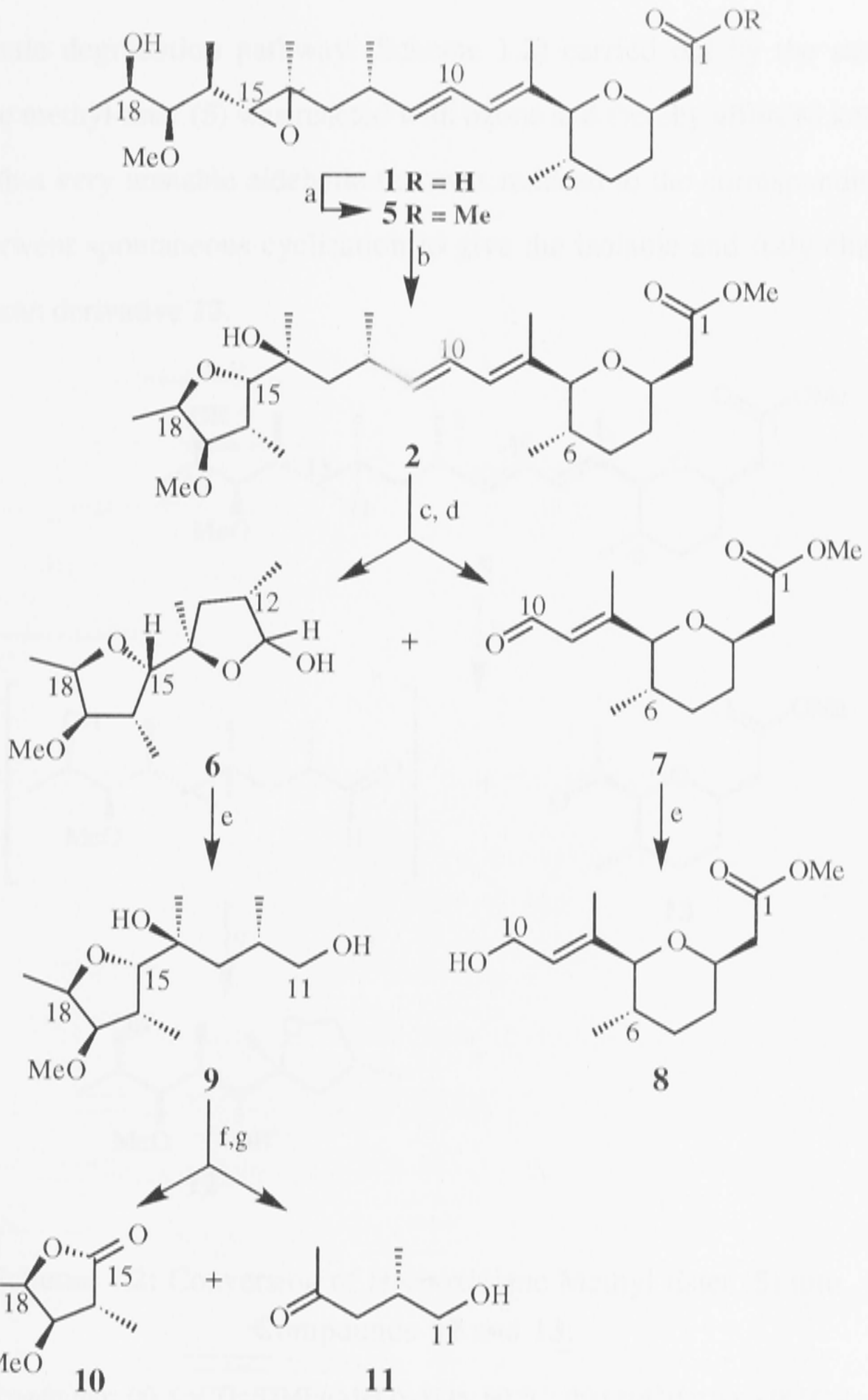


Figure 1.2: Structure-Activity-Relationships within the Herboxidiene Framework. (Arrows Show Rearrangement Pathways Leading to Inactive Compounds)

1.2 Degradation and Synthetic Studies Leading to the Determination of the Structure of Herboxidiene

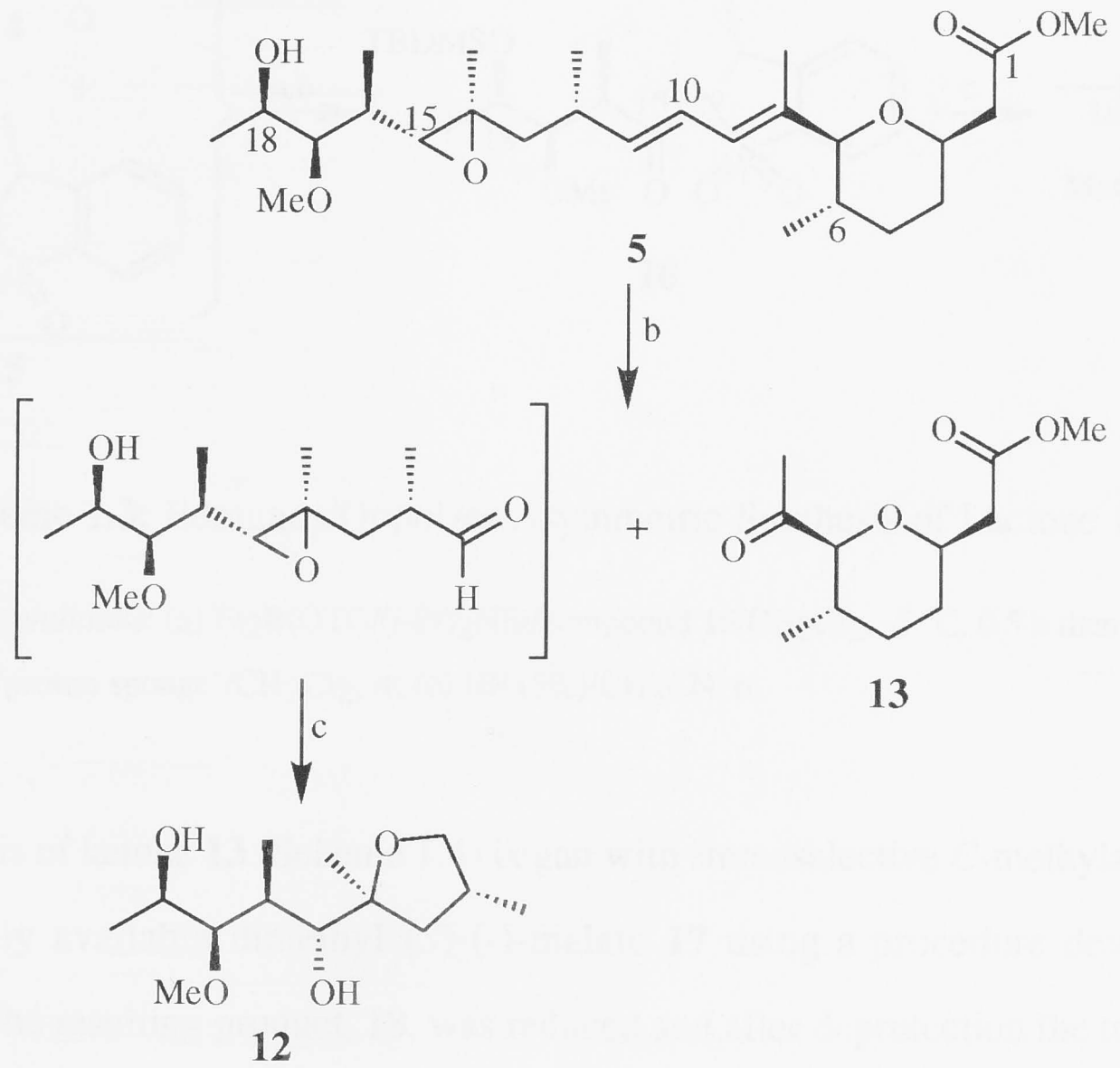
The complete structure of herboxidiene was published in 1997 by A. J. F. Edmunds and his colleagues[5] at Novartis AG, Switzerland. This determination was achieved through, *inter alia*, a combination of selective degradation and chemical correlation studies. One sequence of reactions used for the conversion of herboxidiene into simpler fragments is outlined in Scheme 1.1. Thus, in an early step the tetrahydrofuran derivative **2** was obtained by the HCl-catalysed intramolecular opening of the epoxide-ring within **1** by the 18-hydroxyl functionality. Compound **2** was then regioselectively dihydroxylated at the less hindered $\Delta^{10,11}$ - double bond and the resulting diol subjected to oxidative-cleavage to give two fragments, the α, β-unsaturated aldehyde **7** and the 2,2'-linked *bis*-tetrahydropyran **6**. Each of these degradation products was reduced to the corresponding alcohol, *viz.* compounds **8** and **9** respectively, under standard conditions. The primary alcohol moiety within the latter product was selectively protected and the resulting silyl ether was subjected to further oxidative cleavage to form two new degradation products namely, lactone **10** and ketone **11**.



Scheme 1.1: Degradation Sequences Carried out by Edmunds *et al*[5] in Connection with the Elucidation of the Structure of Herboxidiene (**1**).

Reagents and conditions: (a) K_2CO_3/DMF/$(MeO)_2SO_2$, 90 °C; (b) HCl/MeOH, 0 °C; (c) *N*-methyl morpholine *N*-oxide (NMO)/OsO_4/acetone-H_2O, rt; (d) $NaIO_4$/H_2O-THF, rt; (e) $NaBH_4$/THF-MeOH, 0 °C to rt; (f) TBDPSCl, imidazole, DMAP/DMF, 0 °C to rt; (g) PCC, 4 Å molecular sieves/CH_2Cl_2, reflux.

In an alternate degradation pathway (Scheme 1.2) carried out by the same group, herboxidiene methyl ester (**5**) was reacted with ozone and thereby afforded keto-ester **13** together with a very unstable aldehyde that was reduced to the corresponding alcohol which underwent spontaneous cyclisation to give the isolable and fully characterised tetrahydrofuran derivative **12**.

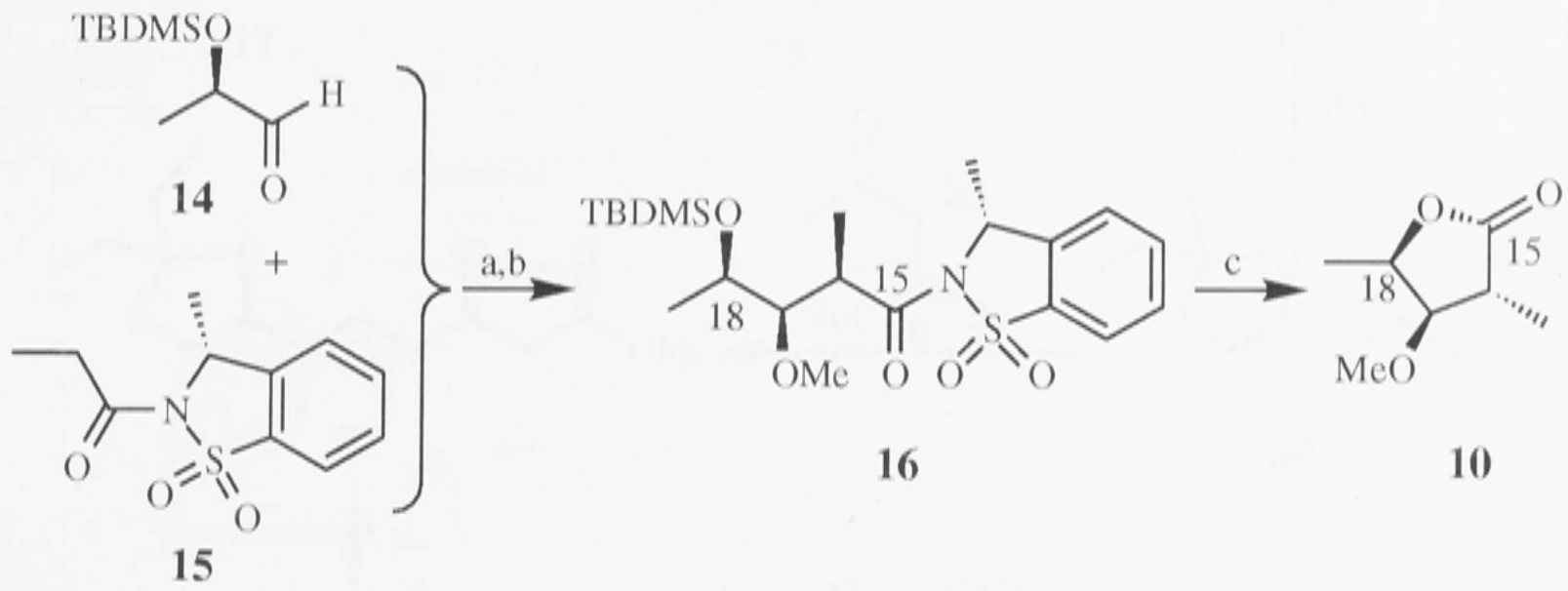


Scheme 1.2: Conversion of Herboxidiene Methyl Ester (**5**) into Compounds **12** and **13**.

Reagents and conditions: (a) K_2CO_3/DMF/$(MeO)_2SO_2$, 90 °C; (b) O_3/CH_2Cl_2, -78 °C then DMS; (c) $NaBH_4$/MeOH/THF, rt.

In order to determine the absolute configuration of herboxidiene both degradation products **10** and **13** were the subject of asymmetric synthesis studies. To these ends, the enantiomerically pure and readily available (*R*)-aldehyde **14** (Scheme 1.3) was subjected to an aldol condensation with the boron enolate derived from sultam **15**. After *O*-methylation of the resulting β-hydroxy ketone with trimethyloxonium tetrafluoroborate

compound **16** was obtained in diastereoisomerically pure form. Deprotection of this last compound with 5% HF resulted in direct cyclisation to the target lactone **10**. This synthetic material proved to be identical, in all respects - including specific rotation, with the sample obtained by degradation of herboxidiene.

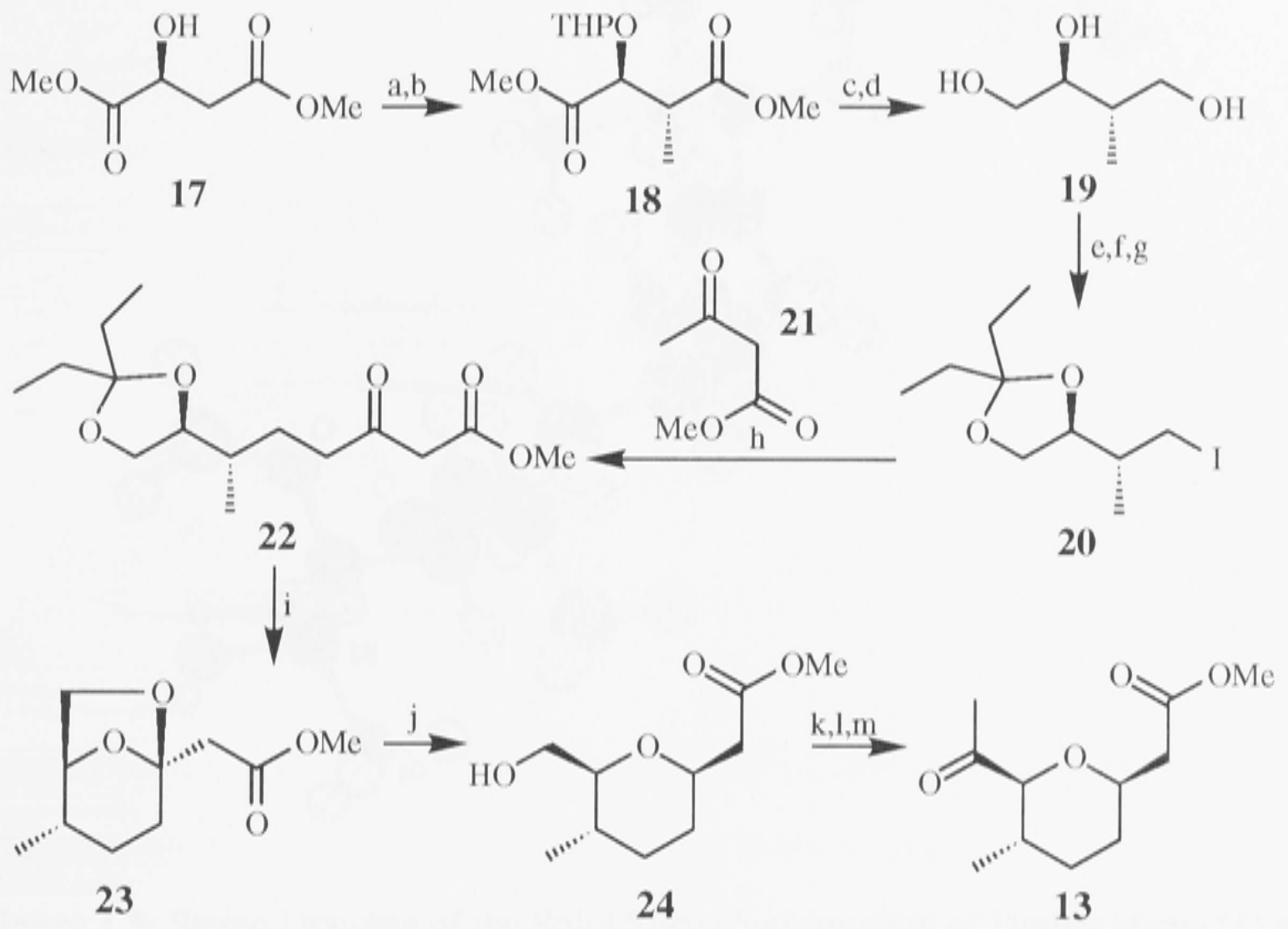


Scheme 1.3: Edmunds/Oppolzer Asymmetric Synthesis of Lactone **10**.

Reagents and conditions: (a) $Et_2B(OTf)/(i\text{-}Pr)_2NEt$/compound **15**/$CH_2Cl_2$, -5 °C, 0.5 h then add **14**; (b) $Me_3O^+BF_4^-$/"proton sponge"/CH_2Cl_2, rt; (c) HF (5%)/CH_3CN, rt.

The synthesis of ketone **13** (Scheme 1.4) began with stereoselective *C*-methylation of the commercially available dimethyl (*S*)-(-)-malate **17** using a procedure developed by Seebach.[7] The resulting product, **18**, was reduced and after deprotection the triol **19** was obtained. Selective protection of the *vic*-diol moiety within this last compound was successfully carried out by using 3-pentanone in the presence of *p*-TsOH and the remaining free (primary) alcohol moiety within product **19** was converted, by standard methods, into the corresponding iodide **20**. Reaction of compound **20** with the dianion of methyl acetoacetate **21** then afforded the β-ketoester **22**. Subsequent deprotection of the last compound led to the formation of the internal and bicyclic acetal **23** which was regioselectively cleaved to the desired alcohol **24**. This alcohol was then subjected to a chain extension sequence involving Swern oxidation, reaction of the resulting aldehyde with methyl magnesium bromide and Jones oxidation of the ensuing mixture of secondary alcohols which afforded the target ketone **13**. Once again, compound **13**, as

obtained by synthesis, was identical in all respects - including specific rotation, with the sample obtained by degradation of herboxidiene.



Scheme 1.4: Edmunds/Oppolzer Synthesis of the Tetrahydropyranyl Core, **13**, of Herboxidiene (**1**).

Reagents and conditions: (a) LDA/MeI/THF, -78 °C; (b) *p*-TsOH, dihydropyran/CH_2Cl_2, rt; (c) $LiAlH_4/Et_2O$, 0 °C; (d) IR-120/MeOH, rt; (e) *p*-TsOH/3-pentanone/THF, reflux, then separation by flash chromatography; (f) *p*-TsCl/Pyr, 0 °C to rt; (g) NaI/acetone, reflux; (h) LDA/THF/HMPA/**21**, 0 °C then add **20**; (i) *p*-$TsOH/CH_2Cl_2$, reflux; (j) $Et_3SiH/TiCl_4/CH_2Cl_2$, -78 °C to -25 °C; (k) $DMSO/(COCl)_2/CH_2Cl_2$ -78 °C then add **24**, Et_3N, -78 °C to rt; (l) $MeMgBr/Et_2O$, -78 °C to -40 °C; (m) CrO_3/H_2SO_4/acetone, rt.

Edmunds' group established the relative stereochemistries of the substituents associated with the herboxidiene framework by X-ray analysis of crystals of the natural product obtained from methylene chloride/methanol. A stereoview of the molecule as observed in the solid state is shown in Figure 1.3.[5]

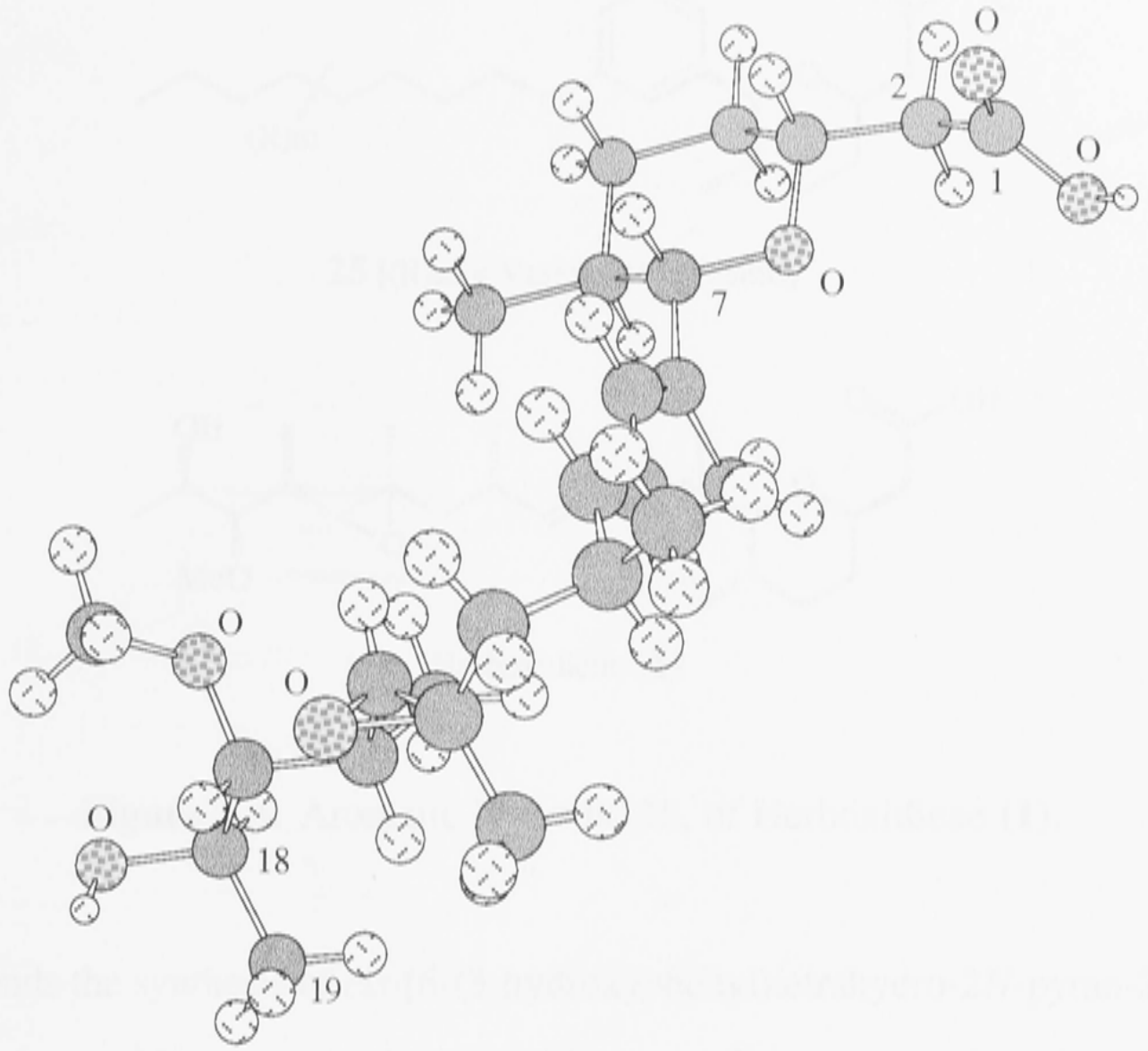
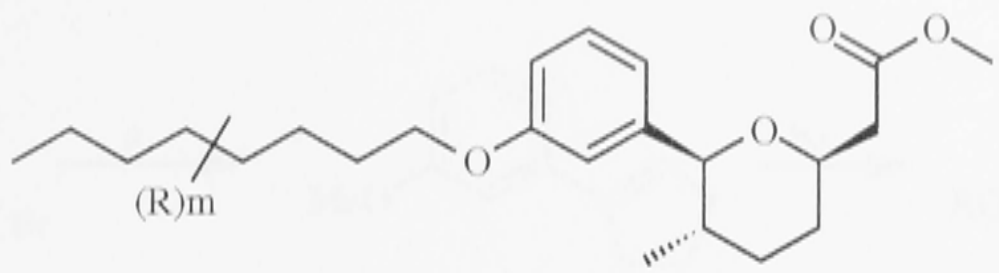


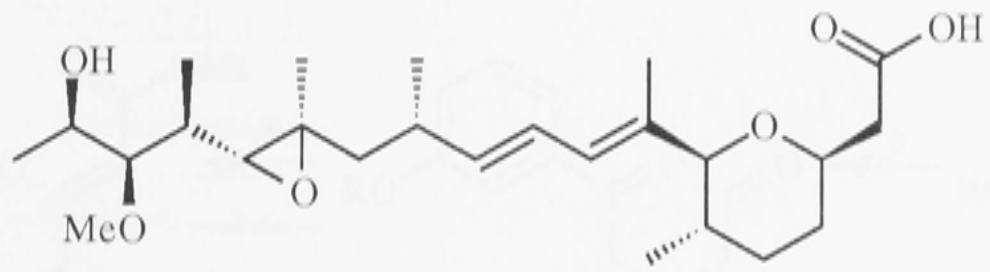
Figure 1.3: Stereo Drawing of the Solid State Conformation of Herboxidiene (**1**) as Determined by Single-crystal X-ray Analysis.

1.3 Synthetically-derived Aromatic Hybrids of Herboxidiene

The synthesis of simplified aromatic hybrids of herboxidiene (Figure 1.4) has been described very recently by Edmunds and his colleagues.[6] In undertaking this work they envisaged that replacement of the sensitive (*E*,*E*)-diene moiety associated with herboxidiene by a phenolic ring, and subsequent attachment of various side chains, *via* the ether linkages to the phenolic oxygen, would provide more stable and structurally simpler (and therefore synthetically accessible) analogues of herboxidiene that would still retain the biological activity.



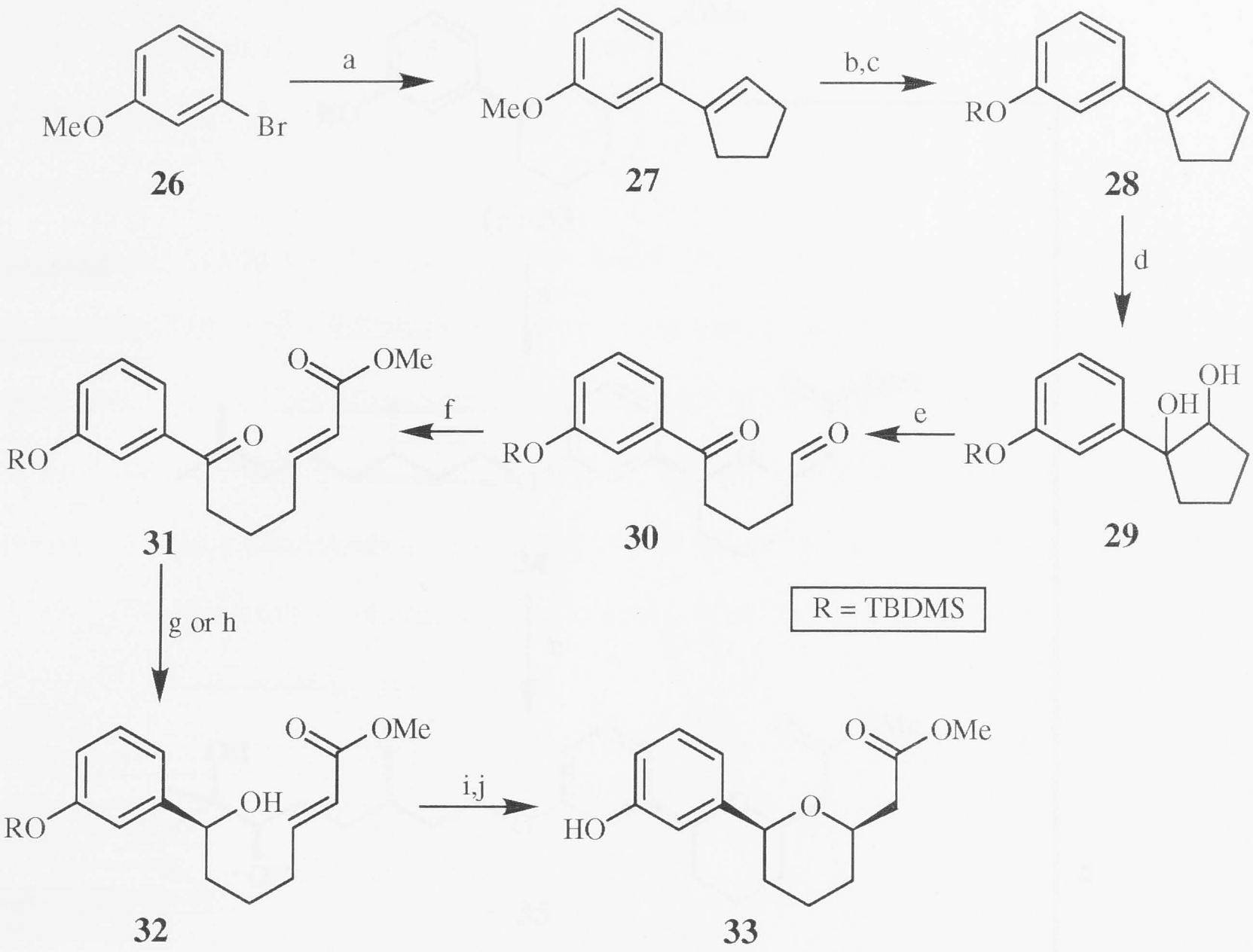
25 [(R)m = Various Side Chains]



Herboxidiene (**1**)

Figure 1.4: Aromatic Hybrids, **25**, of Herboxidiene (**1**).

To these ends the synthesis of *cis*-[6-(3-hydroxyphenyl)tetrahydro-2*H*-pyran-2-yl]acetic acid methyl ester **33** was undertaken and this material was obtained by the route shown in Scheme 1.5. The reaction sequence involved, as the key step, intramolecular and hetero-Michael addition of a hydroxyl group to a tethered acrylate. Several simple side chains were then attached to compound **33** *via* the phenolic oxygen and this step was followed by straightforward manipulations of the resulting products as shown in Scheme 1.6. Of the compounds **35**-**38** produced by this means the last one showed significant herbicidal activity, controlling biannual weeds at an application rate of 1 kg hectare^{-1}. Although herboxidiene methyl ester is 100% effective at this application rate,[1b] these results would never-the-less indicate that the diene moiety of herboxidiene itself can be mimicked by a phenolic ring system.

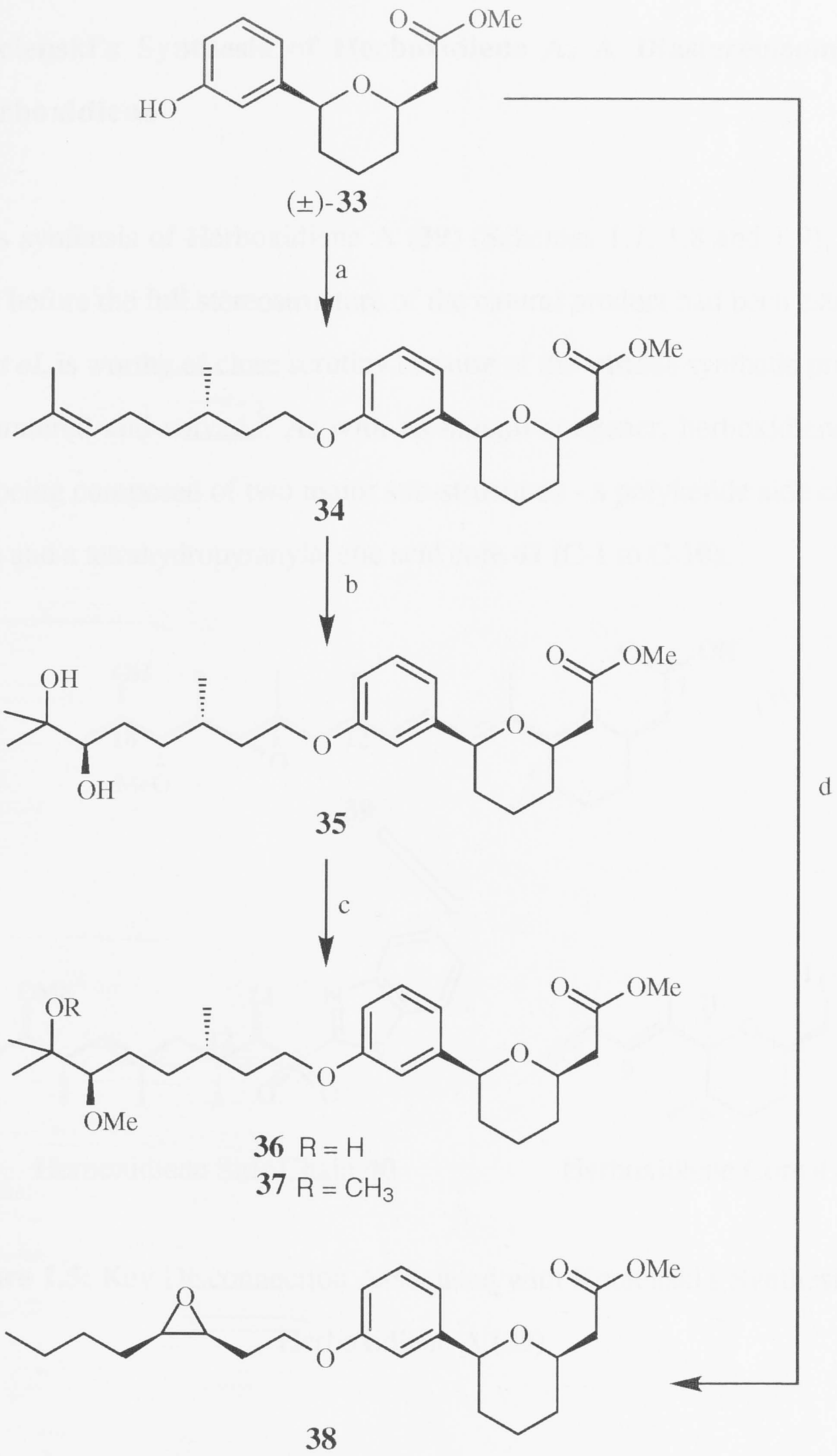


26 **27** **28** **29** **30** **31** **32** **33**

[(±) and (-) forms available; see caption below]

Scheme 1.5: Synthesis of *cis*-[6-(3-Hydroxyphenyl)tetrahydro-2*H*-pyran-2-yl]Acetic Acid Methyl Ester (**33**).

Reagents and conditions: (a) (i) Mg, THF, cyclopentanone, rt; (ii) aqueous HCl; (b) pyridinium.HCl, neat, 150 °C; (c) TBDMSCl, Et_3N, DMAP (cat), CH_2Cl_2, 0 °C to rt; (d) *N*-Methylmorpholine *N*-oxide, OsO_4 (cat), acetone:H_2O (3:1), rt; (e) $NaIO_4$, THF:H_2O (4:1), rt; (f) $Ph_3P{=}CHCO_2Me$, THF, rt; (g) $NaBH_4$, THF, rt **or** (h) (-)-IpC_2BCl, THF, -25 °C; (i) NaH, THF, rt; (j) 95:5 v/v HF (40% in H_2O)/CH_3CN.

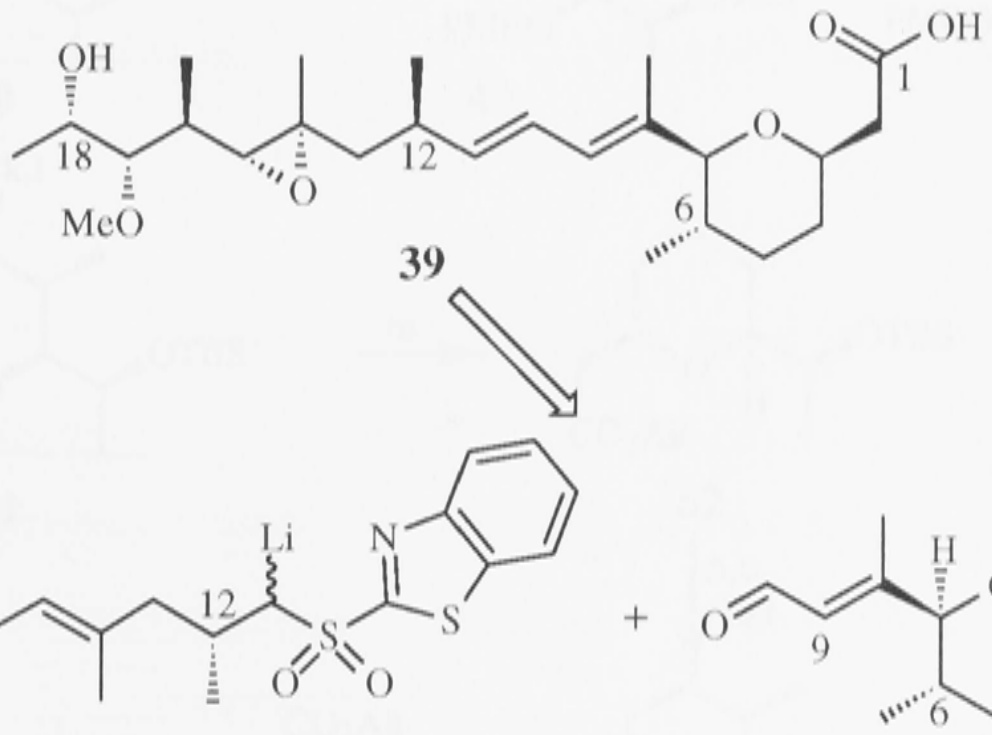


Scheme 1.6: Synthesis of Herboxidiene Mimics **35-38**.

Reagents and conditions : (a) (*S*)- $(CH_3)_2C{=}CHCH_2CH_2CH(CH_3)CH_2CH_2OSO_2Me$, NaH, DMF, 0 °C to rt; (b) AD-mix-β, 1:1 v/v *t*-BuOH/H_2O, 0°C to rt; (c) Ag_2O, MeI, DMF, 50 °C; (d) (3*R*,4*R*)-$CH_3(CH_2)_3CH(O)CHCH_2CH_2OSO_2Me$, NaH, DMF, 0 °C to rt.

1.4 Kocienski's Synthesis of Herboxidiene A, A Diastereoisomer of Herboxidiene

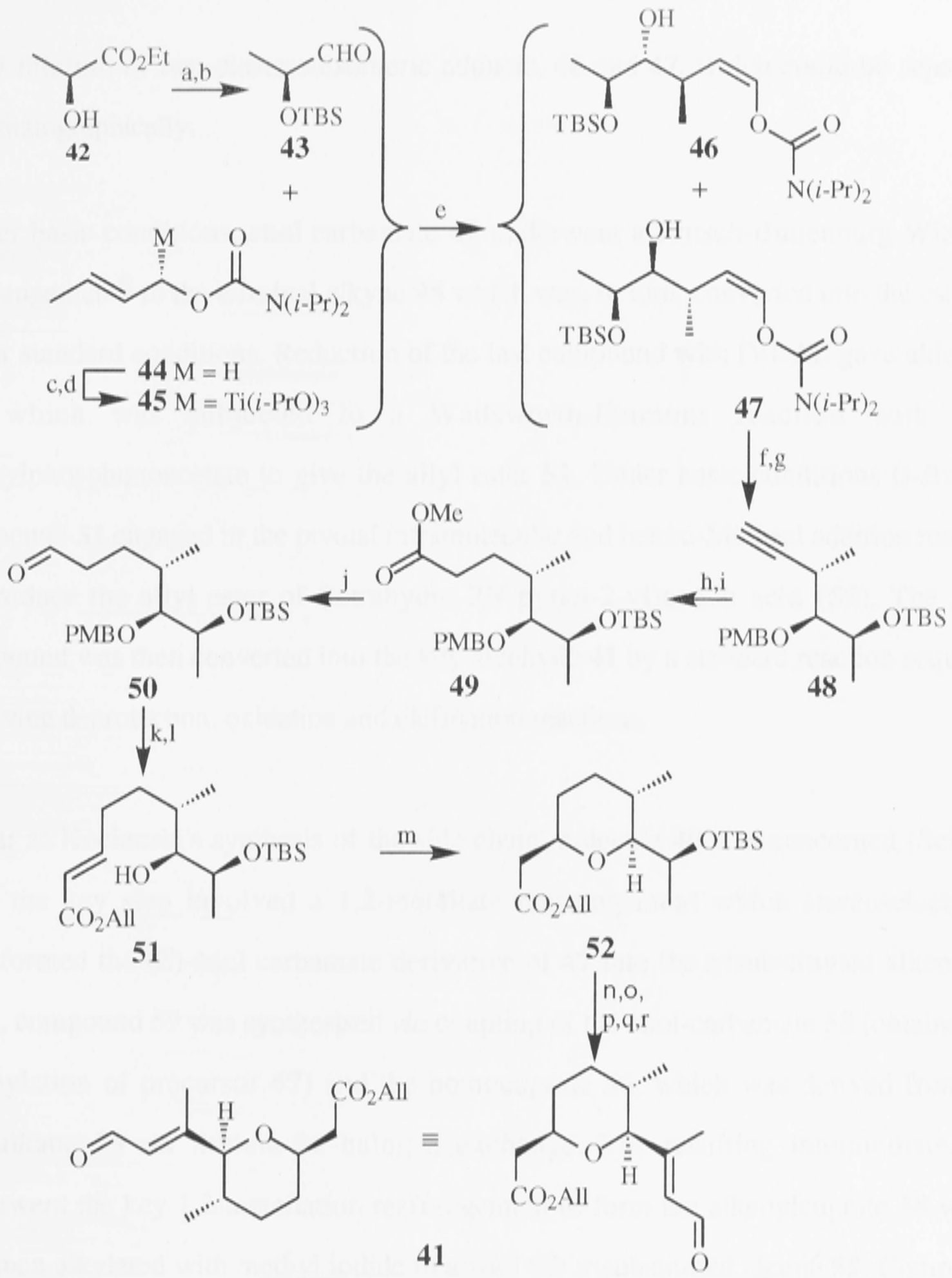
Kocienski's synthesis of Herboxidiene A (**39**) (Schemes 1.7, 1.8 and 1.9), which was undertaken before the full stereostructure of the natural product had been established by Edmunds *et al*, is worthy of close scrutiny because of the various synthetic problems that were encountered and solved.[8] As with its natural congener, herboxidiene A can be viewed as being composed of two major sub-structures - a polyketide side chain **40** (C-11 to C-19) and a tetrahydropyranylacetic acid core **41** (C-1 to C-10).



Herboxidiene Side Chain **40** Herboxidiene Core **41**

Figure 1.5: Key Disconnection Associated with Kocienski's Synthesis of Herboxidiene A (**39**).

Kocienski's synthesis of the core **41** began (Scheme 1.7) with preparation of enol carbamate **47** *via* a Hoppe homo-aldol reaction. Thus, the starting crotyl carbamate **44** was first metallated with BuLi/(-)-sparteine to give a diastereomerically pure complex which was then converted into a configurationally stable conjugate with Ti(O-*i*-Pr)4. This conjugate, **45**, was condensed with the aldehyde **43** which could be readily obtained from the commercially available ethyl (*R*)-(+)-lactate **42**. The condensation reaction led to



Scheme 1.7: Kocienski's Synthesis of the Herboxidiene A Core **41**.

Reagents and conditions : (a) TBSCl, DMAP, imidazole/CH_2Cl_2, rt, 2 h; (b) DIBAL/toluene-CH_2Cl_2, -80 °C (c) BuLi, (-)-sparteine/cyclohexane-pentane, -80 °C, 3 h; (d) Ti(O-*i*-Pr)4/pentane, -80 °C, 20 min; (e) **43** and **45**, -80 °C (1.5 h) to rt (1 h); (f) PMBO-C(=NH)CCl_3, TMSOTf/Et_2O, rt; (g) *t*-BuLi/Et_2O, -20 °C; (h) BuLi/THF, -80 °C then $ClCO_2Me$; (i) H_2 (1 atm), Pd-C/EtOAc, rt; (j) DIBAL/CH_2Cl_2, -80 °C; (k) $(EtO)_2P(=O)CH_2CO_2All$, NaH/THF, -10 °C; (l) DDQ/CH_2Cl_2-H_2O, rt; (m) *t*-BuOK/THF, -65 °C; (n) TBAF, 4 Å molecular sieves/THF, rt; (o) PCC, 4 Å molecular sieves/CH_2Cl_2, rt; (p) $(EtO)_2P(=O)CH_2CO_2Bu^t$, NaH/THF, 0 °C to rt; (q) TFA, PhSMe/CH_2Cl_2; (r) $[Me_2N=CHCl]Cl$/THF-MeCN then $LiAlH(OBu^t)_3$.

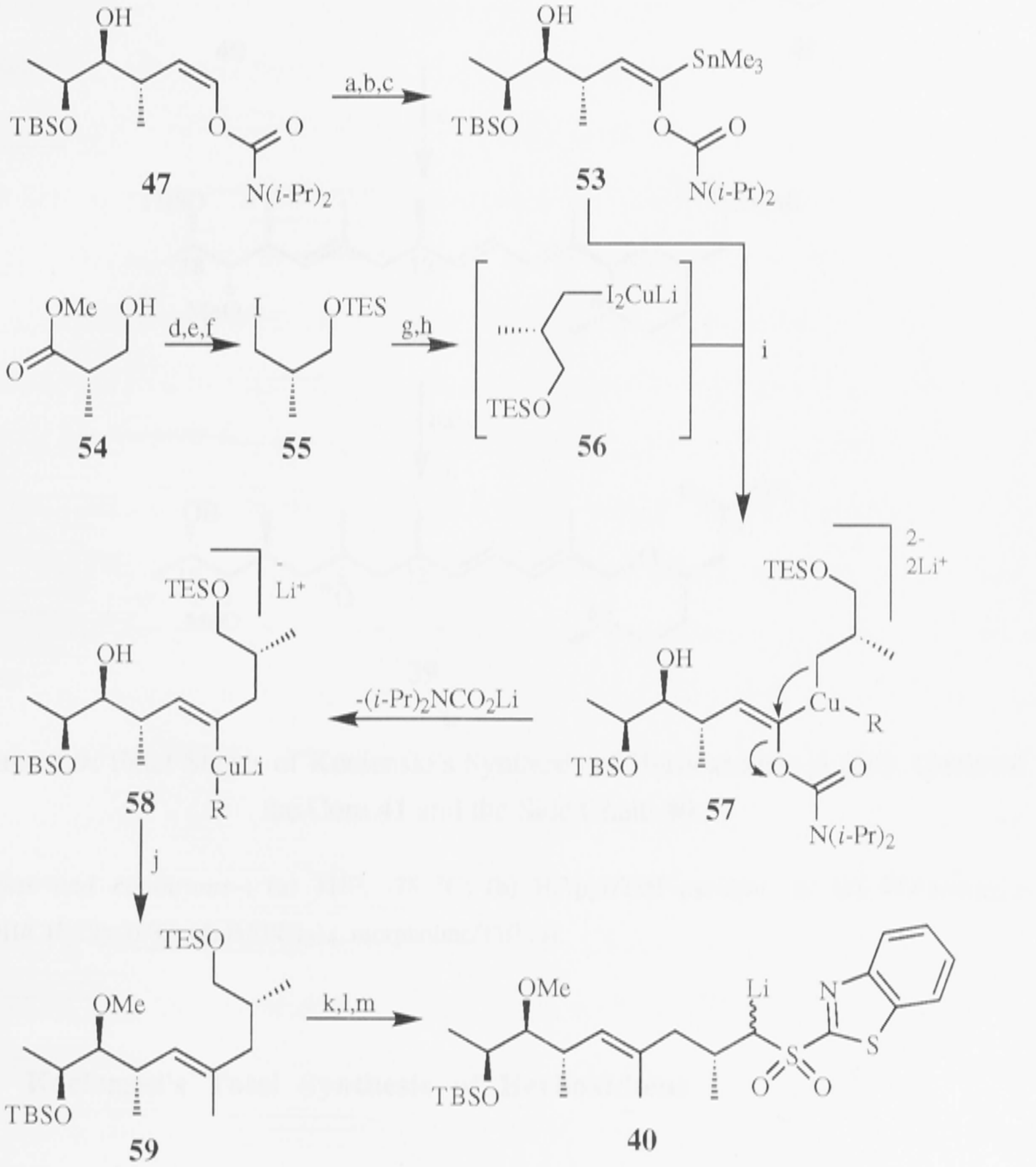
a 1:7 mixture of two diastereoisomeric adducts, **46** and **47**, which could be separated chromatographically.

Under basic conditions, enol carbamate **47** underwent a Fritsch-Buttenburg-Wiechell rearrangement[8] to the terminal alkyne **48** which was, in turn, converted into the ester **49** under standard conditions. Reduction of the last compound with DIBAL gave aldehyde **50** which was subjected to a Wadsworth-Emmons reaction with allyl diethylphosphonoacetate to give the allyl ester **51**. Under basic conditions (*t*-BuOK) compound **51** engaged in the pivotal intramolecular and hetero-Michael addition reaction to produce the allyl ester of (tetrahydro-2*H*-pyran-2-yl)acetic acid (**52**). The latter compound was then converted into the key aldehyde **41** by a standard reaction sequence involving deprotection, oxidation and olefination reactions.

As far as Kocienski's synthesis of the side chain molecule **40** was concerned (Scheme 1.8), the key step involved a 1,2-metallate rearrangement which stereoselectively transformed the (*Z*)-enol carbamate derivative of **47** into the trisubstitiuted alkene **59**. Thus, compound **59** was synthesised *via* coupling of the enol-carbamate **53** (obtained by stannylation of precursor **47**) and the homocuprate **56**, which was derived from the iodoalkane **55** *via* lithium-for-halogen exchange. The resulting intermediate, **57**, underwent the key 1,2-metallation rearrangement to form the alkenylcuprate **58** which was then alkylated with methyl iodide to afford the trisubstituted alkene **59**. Compound **55** was obtained from the commercially available (*S*)-3-hydroxy-2-methylpropionate (**54**) by a previously published and straightforward method.[8] In order to connect the side chain to the core, compound **59** was converted into the sulfone-stabilised anion **40** by standard means.

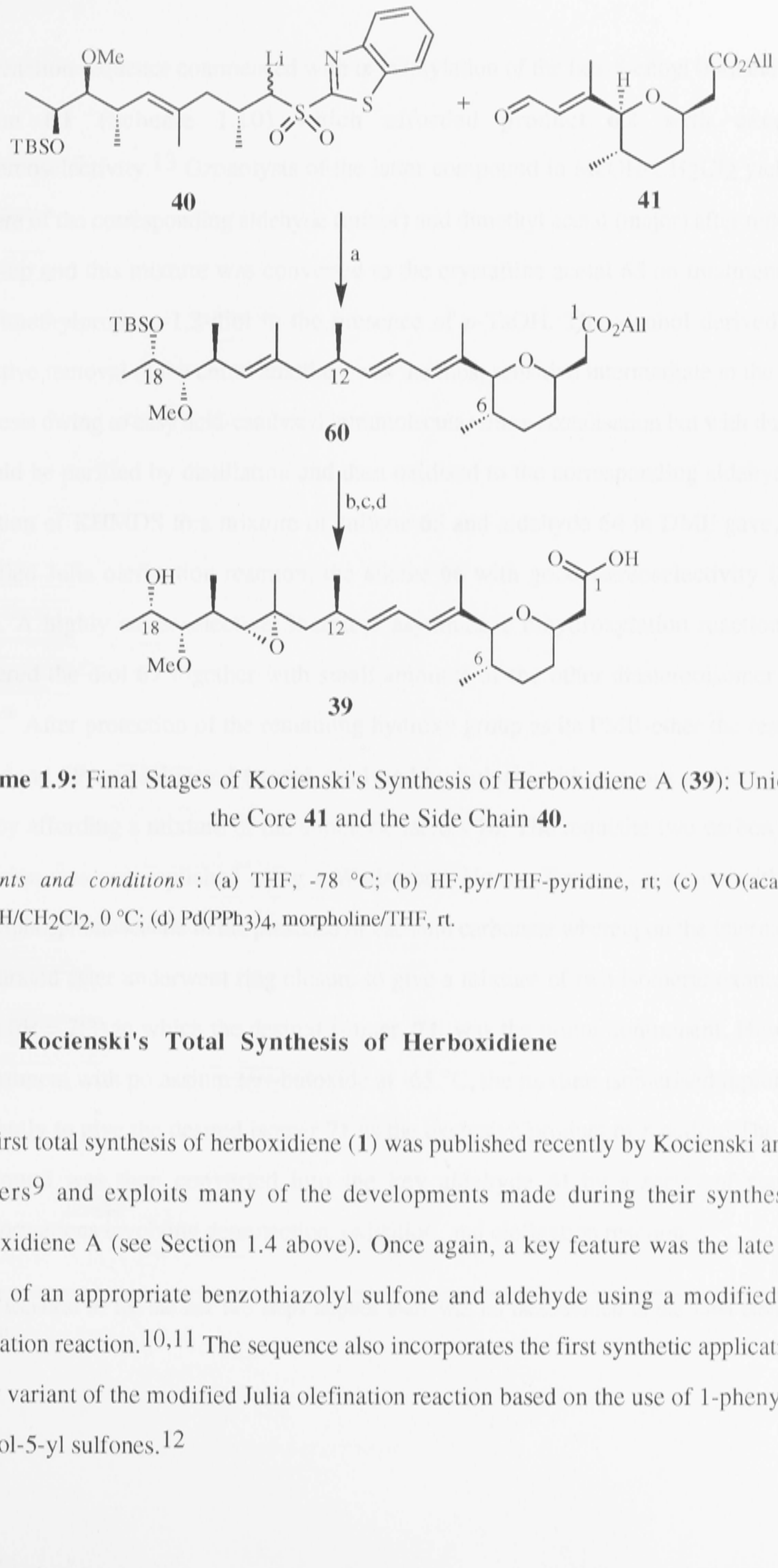
Completion of the synthesis of herboxidiene A (**39**) (Scheme 1.9) was accomplished *via* a modified one-pot Julia olefination reaction involving coupling of anion **40** with the core

aldehyde **41**. Product **60** was then stereoselectively epoxidised with *tert*-butylhydroperoxide in the presence of $VO(acac)_2$. Subsequent allyl-ester deprotection then furnished the target compound, *viz*. herboxidiene A (**39**).



Scheme 1.8: Kocienski's Synthesis of the Herboxidiene A Side Chain **40**.

Reagents and conditions: (a) 4-Me-2,6-di-*t*-Bupyr, MeOTf/toluene, 70 °C; (b) *t*-BuLi/THF, -85 °C, rt; (c) Me_3SnCl, -85 °C, rt; (d) TESCl, DMAP, imidazole/CH_2Cl_2, rt; (e) DIBAL/toluene, -78 °C; (f) I_2, PPh_3, imidazole/CH_2Cl_2, rt; (g) *t*-BuLi/Et_2O-pentane, -80 °C; (h) $CuBr.Me_2S$, Me_2S-THF; (i) **53**, -35 to 0 °C; (j) MeI, HMPA/THF, -20 °C; (k) HF-pyridine/pyridine-THF, 0 °C to rt, 1 h; (l) 2-mercaptobenzothiazole, PPh_3, DEAD/THF, rt, 30 min; (m) $Mo(NH_4)_6$, H_2O_2/EtOH-H_2O, 0 °C to rt 5 h, rt, 24 h.



Scheme 1.9: Final Stages of Kocienski's Synthesis of Herboxidiene A (**39**): Union of the Core **41** and the Side Chain **40**.

Reagents and conditions : (a) THF, -78 °C; (b) HF.pyr/THF-pyridine, rt; (c) $VO(acac)_2$, *t*-$BuOOH/CH_2Cl_2$, 0 °C; (d) $Pd(PPh_3)_4$, morpholine/THF, rt.

1.5 Kocienski's Total Synthesis of Herboxidiene

The first total synthesis of herboxidiene (**1**) was published recently by Kocienski and co-workers[9] and exploits many of the developments made during their synthesis of herboxidiene A (see Section 1.4 above). Once again, a key feature was the late stage union of an appropriate benzothiazolyl sulfone and aldehyde using a modified Julia olefination reaction.[10,11] The sequence also incorporates the first synthetic application of a new variant of the modified Julia olefination reaction based on the use of 1-phenyl-1*H*-tetrazol-5-yl sulfones.[12]

The reaction sequence commenced with α-methylation of the hex-5-enoyl bornane-10,2-sultam **61** (Scheme 1.10) which afforded product **62** with excellent diastereoselectivity.[13] Ozonolysis of the latter compound in MeOH-CH_2Cl_2 yielded a mixture of the corresponding aldehyde (minor) and dimethyl acetal (major) after reductive work-up and this mixture was converted to the crystalline acetal **63** on treatment with 2,2-dimethylpropane-1,3-diol in the presence of *p*-TsOH. The alcohol derived from reductive removal of the chiral auxiliary was the most sensitive intermediate in the entire synthesis owing to easy acid-catalysed intramolecular *trans*-acetalisation but with due care it could be purified by distillation and then oxidised to the corresponding aldehyde **64**. Addition of KHMDS to a mixture of sulfone **65** and aldehyde **64** in DME gave, *via* a modified Julia olefination reaction, the alkene **66** with good stereoselectivity (*E*:*Z* = 93:7). A highly stereoselective Sharpless asymmetric dihydroxylation reaction then delivered the diol **67** together with small amounts of the other diastereoisomer (dr = 93:7).* After protection of the remaining hydroxy group as its PMB-ether the resulting compound **69** was subjected to acid-catalysed hydrolysis with aqueous acetic acid and thereby affording a mixture of the anomeric lactols **70**. The requisite two-carbon chain extension was accomplished using a Wadsworth-Horner-Emmons reaction with allyl diethylphosphonoacetate in the presence of caesium carbonate whereupon the intermediate unsaturated ester underwent ring closure to give a mixture of two isomeric oxaneacetic esters (dr = 2:3) in which the desired isomer, **71**, was the minor component. However, on treatment with potassium *tert*-butoxide at -65 °C, the mixture isomerised rapidly and efficiently to give the desired isomer **71** as the exclusive product of reaction. The latter compound was then converted into the key aldehyde **41** by a series of standard transformations involving deprotection, oxidation, and olefination reactions.

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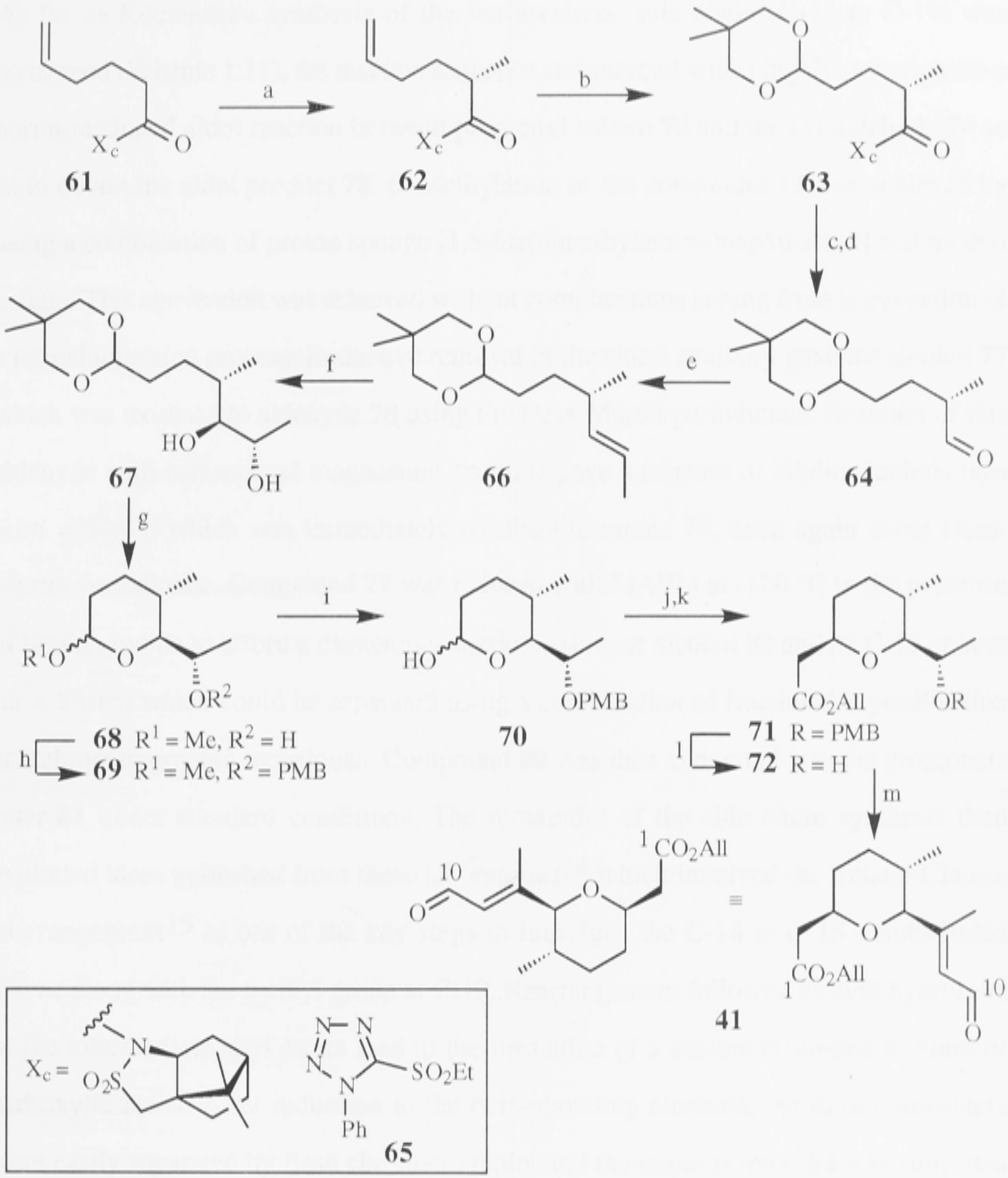
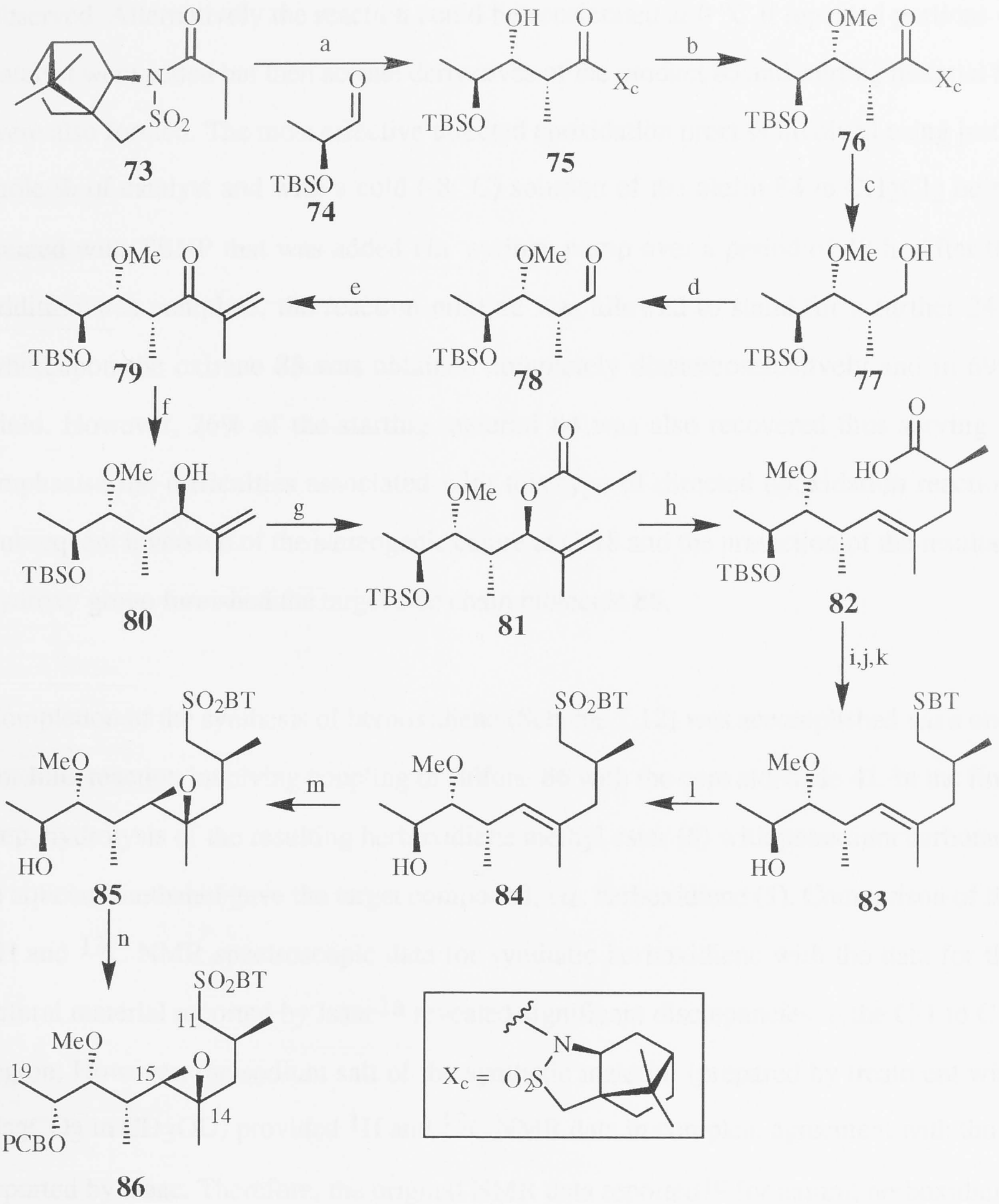
* The identical dr for the last two steps implies there was no racemisation in the Julia olefination reaction.



Scheme 1.10: Kocienski's Synthesis of the C-1 to C-10 Core Fragment **41** of Herboxidiene (**1**)

Reagents and conditions: (a) (i) BuLi, THF, -80 °C, 2 h; (ii) MeI, DMPU, -80 °C to rt, 12 h; (b) (i) O_3, MeOH-CH_2Cl_2 (1:3), -78 °C, 2 h; (ii) Me_2S, -78 °C to rt, 12 h; (iii) 2,2-dimethylpropane-1,3-diol, *p*-TsOH, PhMe, heat, (-H_2O), 12 h; (c) $LiAlH_4$, Et_2O, rt, 12 h; (d) Pyr.SO_3, Et_3N, DMSO, rt, 30 min; (e) sulfone **65**, KHMDS, DME, -60 °C, 45 min; (f) AD-mix α, $MeSO_2NH_2$, *t*-BuOH-H_2O (2:3), 0 °C, 18 h; (g) *p*-TsOH, MeOH, rt, 3d, α : β = 3 :1; (h) (i) KHMDS, THF, 0 °C, 20 min; (ii) PMBCl, TBAI, 0 °C to rt, 24 h; (i) AcOH-THF-H_2O (3 : 2 : 2), 65 °C, 2 h, α : β = 3 :2; (j) allyl diethyl phosphonoacetate, Cs_2CO_3, THF, heat, 18 h; (k) *t*-BuOK, THF, -65 °C, 10 min, pure *cis* isomer; (l) DDQ, 1:15 v/v H_2O/CH_2Cl_2, rt, 30 min; (m) 4 steps (see ref.10).

As far as Kocienski's synthesis of the herboxidiene side chain (C-11 to C-19) was concerned (Scheme 1.11), the reaction sequence commenced with a highly stereoselective boron-mediated aldol reaction between propionyl sultam **73** and the (*S*)-aldehyde **74** so as to obtain the aldol product **75**. *O*-Methylation of the compound **75** was achieved by using a combination of proton sponge [1,8-*bis*(dimethylamino)naphthalene] and methyl triflate. This conversion was achieved without complications arising from intervention of a retroaldolisation process. Reductive removal of the chiral auxiliary gave the alcohol **77** which was oxidised to aldehyde **78** using the Dess-Martin periodinane. Reaction of this aldehyde with isopropenyl magnesium bromide gave a mixture of allylic alcohols (*syn* :*anti* = 57:43) which was immediately oxidised to enone **79**, once again using Dess-Martin periodinane. Compound **79** was reduced with $LiAlH_4$ at -100 °C in the presence of lithium iodide to afford a diastereoisomeric mixture of alcohol **80** and its C-15 epimer (dr = 85:15) which could be separated using a combination of fractional crystallisation and chromatographic techniques. Compound **80** was then converted into the propionate ester **81** under standard conditions. The remainder of the side chain synthesis then exploited ideas published from these laboratories[14] which involved the Ireland-Claisen rearrangement[15] as one of the key steps to introduce the C-14 to C-15 trisubstituted alkene along with the methyl group at C-12. Rearrangement followed by acid hydrolysis of the intermediate silyl esters lead to the formation of a diastereoisomeric mixture of carboxylic acids. After reduction to the corresponding alcohols, the diastereoisomers were easily separated by flash chromatography and the major isomer, **82** was subjected to a Mitsunobu reaction with 2-mercaptobenzothiazole[16] to give the thioether **83** in good yield. The reactivity of an unsaturated alcohol toward $VO(acac)_2$-catalysed epoxidation depends on the proximity of the hydroxy group to the alkene.[17] In fact, this type of oxidation of *bis*-homoallylic alcohol **84** proved to be extremely slow at sub-ambient temperatures and at low catalyst loadings. In addition, when the epoxidation was conducted in toluene at 60 °C [3 mol% $VO(acac)_2$, 1.5 equiv. *tert*-butylhydroperoxide (TBHP)] ring-closure of the product epoxide to a tetrahydrofuran (cf. Scheme 1.1) was



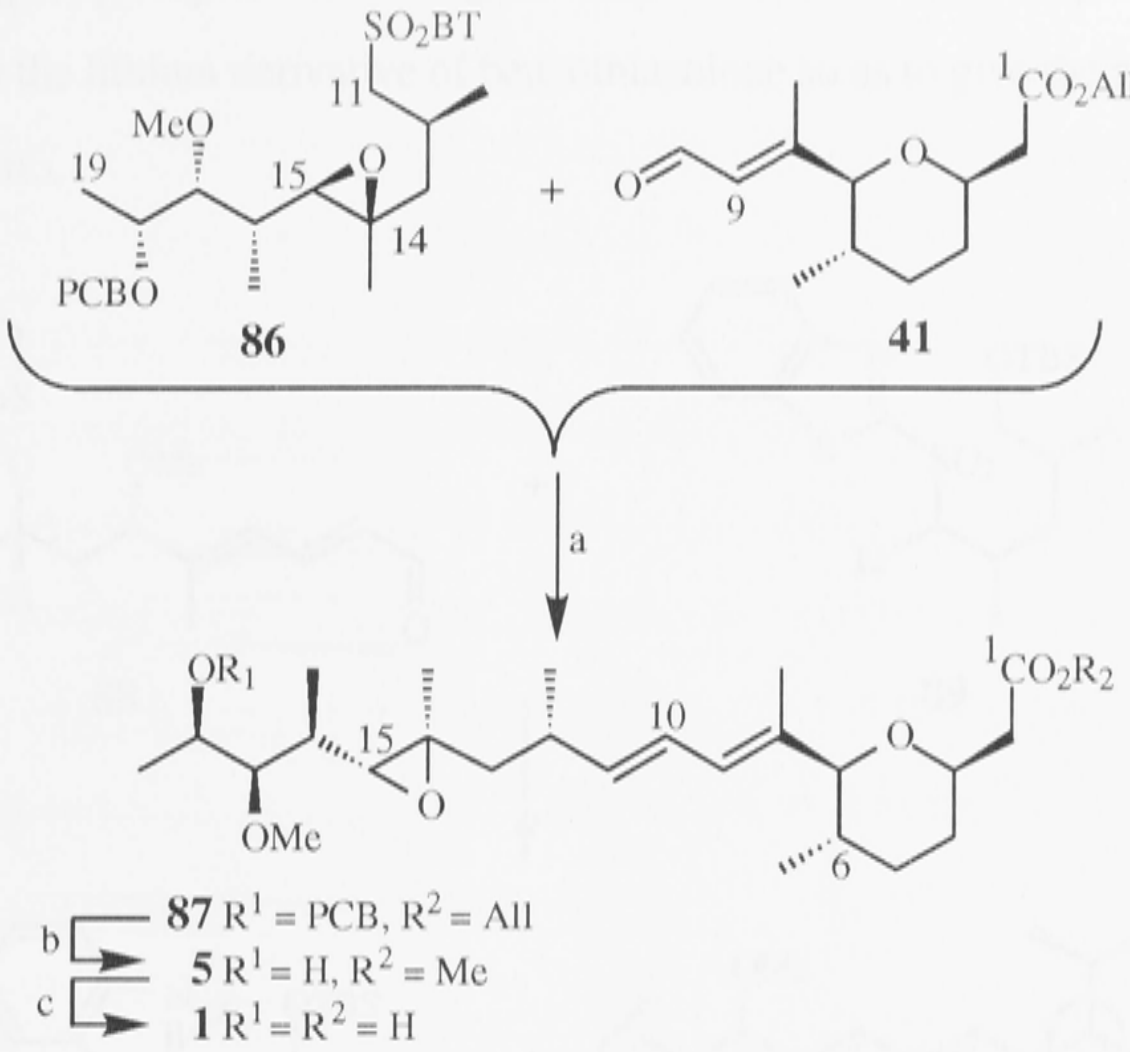
Scheme 1.11: Kocienski's Synthesis of the C-11 to C-19 Side Chain Fragment **86** Associated with Herboxidiene (**1**).

Reagents and conditions: (a) (i) Et_2BOTf, CH_2Cl_2, -5 °C; (ii) *i*-Pr_2NEt, 30 min; (iii) **74**, -78 °C, 3 h; (b) MeOTf, proton sponge, PhMe, 80 °C, 24 h; (c) $LiAlH_4$, Et_2O, 0 °C, 15 min; (d) Dess-Martin periodinane, CH_2Cl_2, 0 °C to rt, 2 h; (e) (i) CH_2=C(Me)MgBr, Et_2O, 0 °C, 1 h; (ii) DMP, CH_2Cl_2, rt, 4 h; (f) $LiAlH_4$, LiI, Et_2O, -100 °C, 1 h; (g) $(EtCO)_2O$, DMAP, pyridine, rt, 16 h; (h) (i) LDA, THF, -78 °C, 30 min; (ii) TBSCl, DMPU; (iii) -78 °C→Δ, 1 h; (iv) aq. HCl; (i) $LiAlH_4$, Et_2O, 0 °C, 10 min; (j) BTSH, Ph_3P, DIAD, THF, 0 °C to rt, 2 h; (k) TBAF.$3H_2O$, THF, rt, 32 h; (l) Mo(vi), H_2O_2, H_2O-EtOH, rt, 24 h; (m) $VO(acac)_2$, TBHP, CH_2Cl_2, -8 °C, 72 h; (n) (i) Ph_3P, DMAD, THF, 0 °C; (ii) PCBOH, 0 °C to rt, 3 h.

observed. Alternatively the reaction could be accelerated at 0 °C if repeated portions of catalyst were added but then acetate derivatives of the product **85** and starting material **84** were also formed. The most effective directed epoxidation process involved using just 1 mole % of catalyst and with a cold (-8 °C) solution of the olefin **84** in CH_2Cl_2 being treated with TBHP that was added *via* syringe pump over a period of 48 h. After the addition was complete, the reaction mixture was allowed to stand for a further 24 h whereupon the oxirane **85** was obtained completely diastereoselectively and in 69% yield. However, 26% of the starting material **84** was also recovered thus serving to emphasise the difficulties associated with this type of directed epoxidation reaction. Subsequent inversion of the stereogenic centre at C-18 and the protection of the resultant hydroxy group furnished the target side chain molecule **86**.

Completion of the synthesis of herboxidiene (Scheme 1.12) was accomplished *via* a one-pot Julia reaction involving coupling of sulfone **86** with the core aldehyde **41**. In the final step, hydrolysis of the resulting herboxidiene methyl ester (**5**) with potassium carbonate in aqueous methanol gave the target compound, *viz.* herboxidiene (**1**). Comparison of the ^{1}H and ^{13}C NMR spectroscopic data for synthetic herboxidiene with the data for the natural material reported by Isaac[1a] revealed significant discrepancies in the C-1 to C-3 region. However, the sodium salt of the synthetic material (prepared by treatment with Na_2CO_3 in CD_3OD) provided ^{1}H and ^{13}C NMR data in complete agreement with those reported by Isaac. Therefore, the original NMR data reported[1c] for natural herboxidiene likely pertains to a carboxylate salt derivative rather than the free acid.

The second Julia-type coupling reaction Kocienski used in his work (Scheme 1.12) allows for creation of the correct (*E*,*E*)-geometry about the $\Delta^{8,9}$- and $\Delta^{10,11}$-double-bonds in target **1**. Further, Kocienski's work has shown that, variation of the heterocyclic sulfone can be used to optimise the yield and stereoselectivity of this type of olefination reaction. The benzo-thiazolyl sulfone unit is superior for the construction of the conjugated (*E*,*E*)-diene moiety whereas a 1-phenyl-1*H*-tetrazol-5-yl sulfone gave high

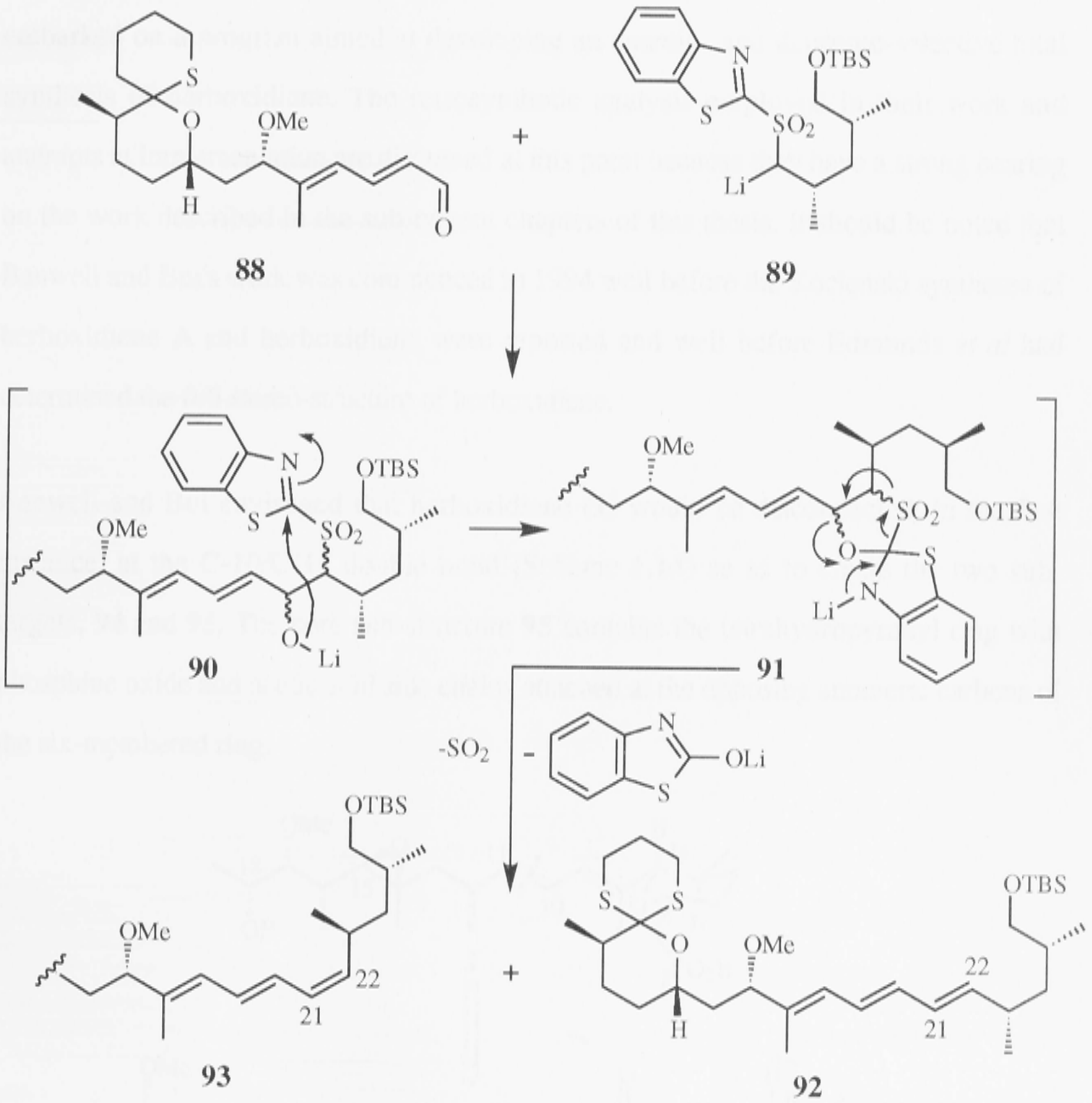


Scheme 1.12: Completion of Kocienski's Synthesis of Herboxidiene - Union of Core **41** and Side Chain **86**.

Reagents and conditions: (a) (i) LDA, THF, -78 °C, 15 min; (ii) **41**, -78 °C to -20 °C, 1.5 h; (b) K_2CO_3, MeOH, Δ, 2 h; (c) K_2CO_3, H_2O-MeOH (1 : 4), Δ, 1 h.

yields and *trans*-selectivity in the construction of a simple alkene. A detailed study of 100 examples revealed some important limitations to the method[10,11] including (i) the fact that high stereoselectivities are only obtained in special cases (e.g. when the formation of conjugated dienes are involved) and, (ii) some lithiated benzothiazolyl sulfones are unstable and undergo self-condensation, even at low temperatures. Interestingly, application of the Julia olefination reaction to the synthesis of the conjugated triene segment of rapamycin[61] (Scheme 1.13) showed that high efficiency and good stereoselectivity can be secured by varying the base and the solvent, with best results being obtained using LiHMDS in a non-polar solvent. Thus, under such reaction conditions the appropriate sulfone was selectively deprotonated and the resultant anion, **89**, underwent reversible addition to the aldehyde. The adduct **90** thus obtained then cyclised *via* addition of the alkoxy anion onto the C=N bond of the benzothiazole unit

thereby leading to spirocycle **91**, the fragmentation of which was accompanied by loss of SO_2 as well as the lithium derivative of benzothiazolone so as to give the alkenes **92** and **93** in a 19:1 ratio.

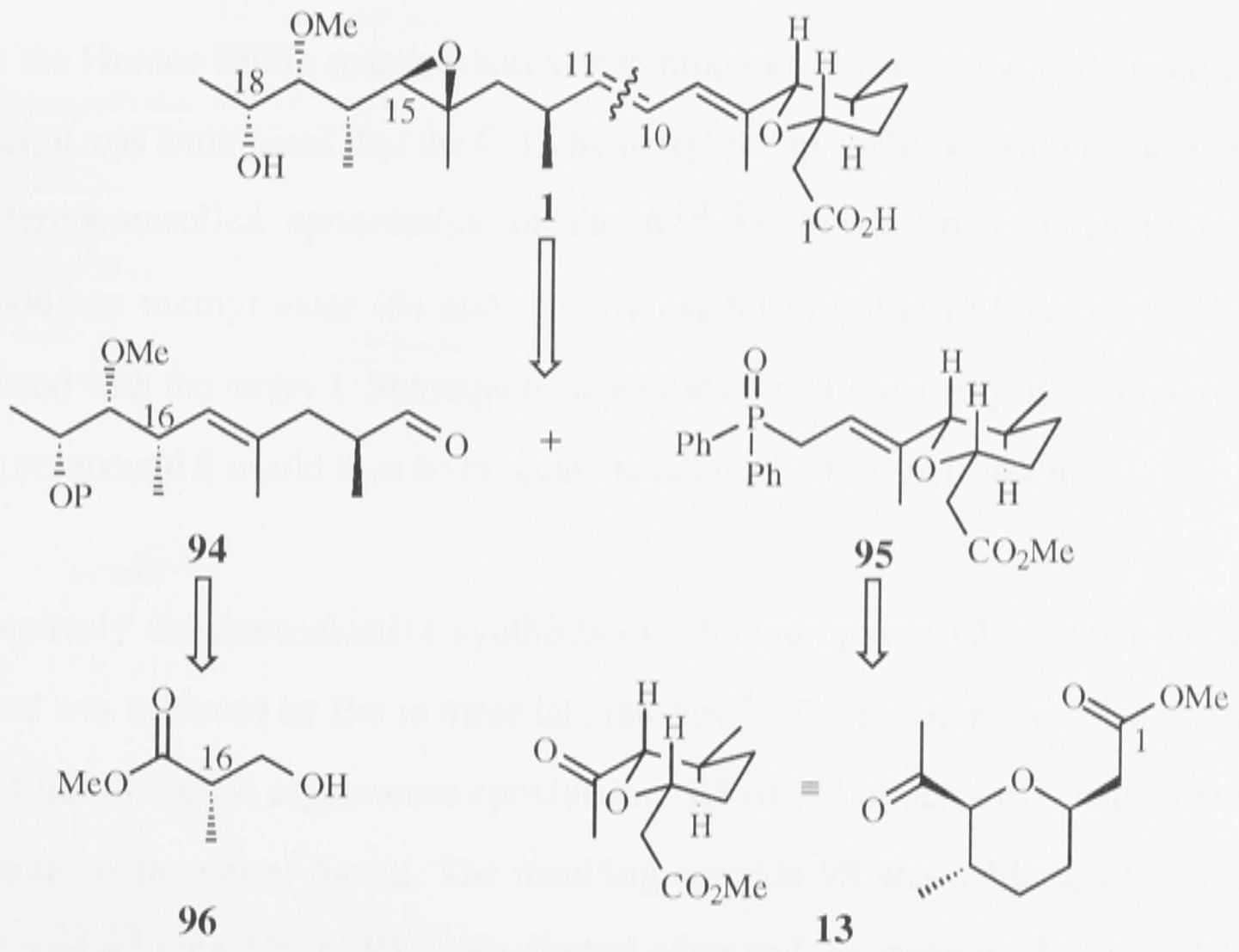


Scheme 1.13: An Example of a One-pot Julia Olefination Reaction as Used in the Synthesis of the Rapamycin Fragment **92**.

1.6 Objectives of the Work Detailed in this Thesis

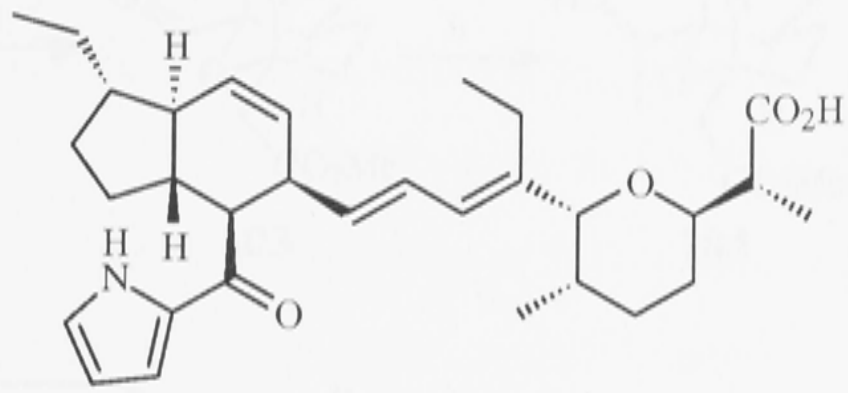
In 1993, in collaboration with Dunlena Pty Ltd, Banwell and Bui, initially located at the University of Melbourne and subsequently at the Australian National University, embarked on a program aimed at developing an enantio- and diastereo-selective total synthesis of herboxidiene. The retrosynthetic analysis employed in their work and attempts at implementation are discussed at this point because they have a strong bearing on the work described in the subsequent chapters of this thesis. It should be noted that Banwell and Bui's work was commenced in 1994 well before the Kocienski syntheses of herboxidiene A and herboxidiene were reported and well before Edmunds *et al* had determined the full stereo-structure of herboxidiene.

Banwell and Bui envisaged that herboxidiene (**1**) would be disconnected, in the first instance, at the C-10/C-11 double bond (Scheme 1.14) so as to create the two sub-targets, **94** and **95**. The core sub-structure **95** contains the tetrahydropyranyl ring with phosphine oxide and acetic acid side chains attached at the opposing anomeric carbons of the six-membered ring.



Scheme 1.14: Banwell and Bui's Retrosynthetic Analysis of Herboxidiene (**1**).

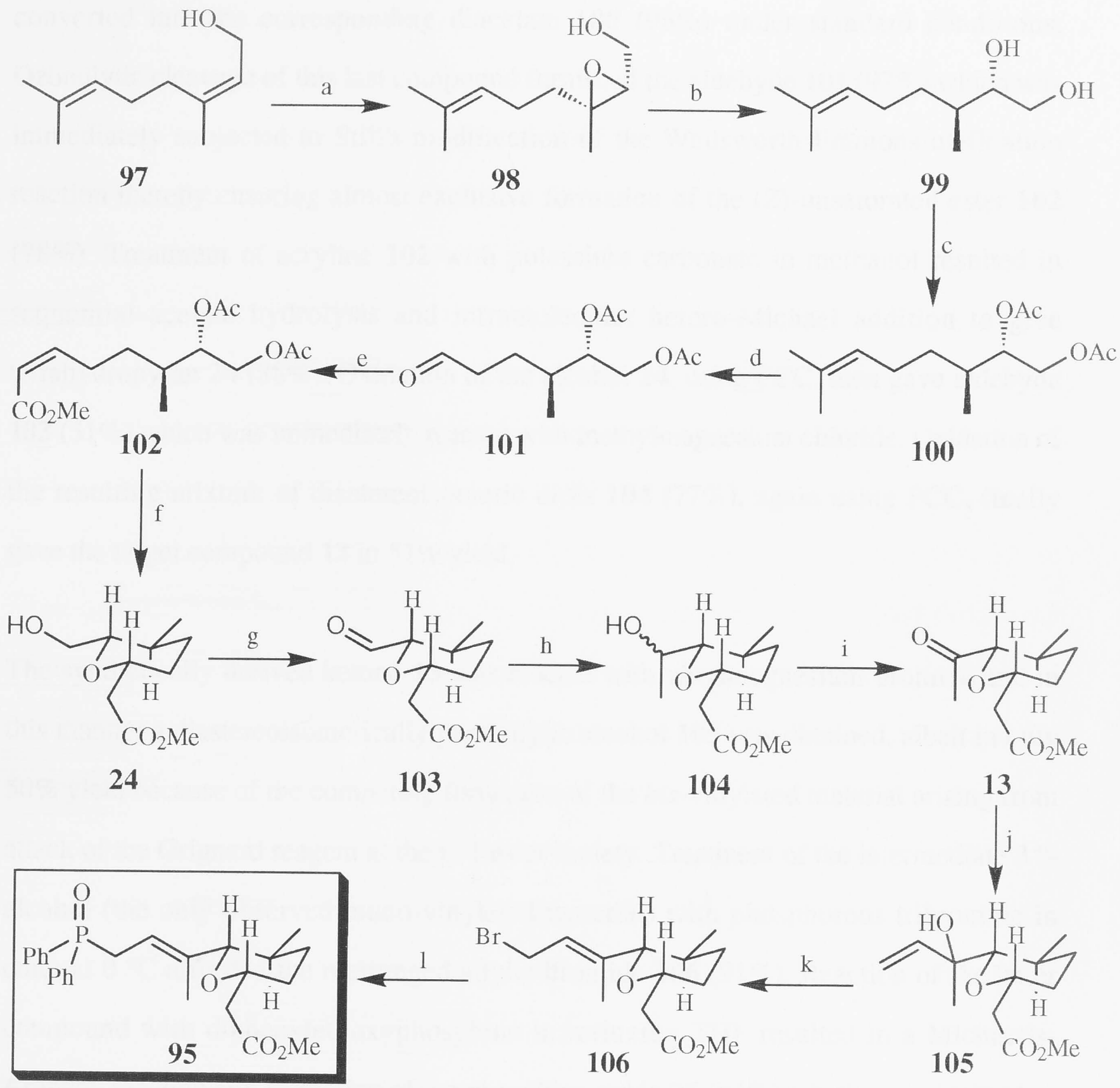
Further disconnection at the remaining double-bond within synthon **95** gives rise to the ketone **13** which was chosen as the initial synthetic target partly because this material had been obtained during the original degradation work carried out on herboxidiene. Compound **94**, which has been called the herboxidiene side chain, is a polyketide based entity containing four centres of asymmetry and it was envisaged that the aldehyde moiety within this synthon could be used for connection to the phosphine oxide **95** under standard Horner-Wittig coupling conditions. This approach is reminiscent of that undertaken by both the Nicolaou[18] and Ley[19] groups in their total syntheses of the ionophore antibiotic indanomycin (a.k.a. X-14547A).



Indanomycin (a.k.a. X-14547A)

While the Horner-Wittig reaction between compounds **94** and **95** would create a triene product, it was anticipated that the C-18 hydroxyl group could be exploited in a directed and stereocontrolled epoxidation of the $\Delta^{14,15}$-double-bond so as to generate herboxidiene methyl ester (**5**) and thereby establishing the full assembly of atoms associated with the target **1**. Subsequent saponification of the methyl ester moiety at C-1 within compound **5** would then be expected to deliver herboxidiene itself.

A completely diastereoselective synthesis of tetrahydropyran **13** is shown in Scheme 1.15 and was achieved by Bui in these laboratories.[20] The reaction sequence began with the Katsuki-Sharpless asymmetric epoxidation (KSAE)[21] of nerol (**97**) using diethyl *D*-(-)-tartrate as the chiral ligand. The resulting epoxide **98** was subjected to reductive-cleavage[22,23] with $NaCNBH_3$-BF_3·diethyl ether and the ensuing diol **99** (73%) then



Scheme 1.15: Enantioselective Route from Nerol (**97**) to Phosphine Oxide **95**.

Reagents and conditions: (a) KSAE, diethyl *D*-(-)-tartrate/CH_2Cl_2; (b) $NaBH_3CN$, $BF_3.OEt_2$/THF; (c) Ac_2O, DMAP (trace)/pyridine, 18 °C; (d) O_3/CH_2Cl_2, -78 °C then PPh_3; (e) $MeO_2CCH_2P(O)(OCH_2CF_3)_2$, 18-crown-6/$CH_3CN$-complex, KHMDS/THF, -78 °C; (f) K_2CO_3/MeOH, rt, then MeOH, H_2SO_4 (trace), rt; (g) PCC, NaOAc/CH_2Cl_2, 18 °C; (h) MeMgCl/THF, 0 °C; (i) PCC, NaOAc/CH_2Cl_2, 18 ° C; (j) $H_2C=C(H)MgBr$/THF, -78 °C; (k) PBr_3/Et_2O, 0 °C; (l) Ph_2POEt/THF, reflux, 2 h.

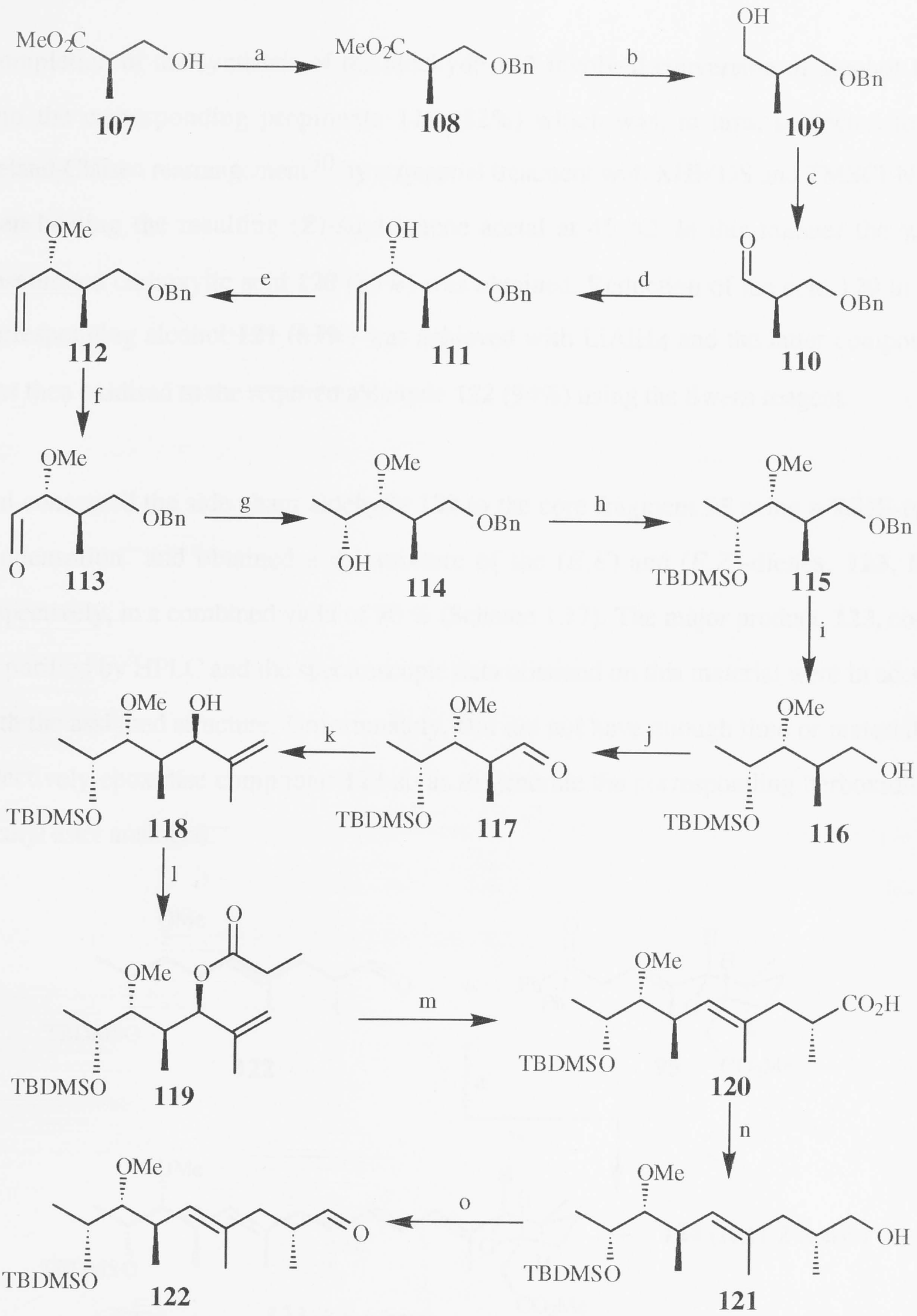
converted into the corresponding diacetate **100** (96%) under standard conditions. Ozonolytic cleavage of this last compound furnished the aldehyde **101** (97%) which was immediately subjected to Still's modification of the Wadsworth-Emmons olefination reaction thereby ensuring almost exclusive formation of the (*Z*)-unsaturated ester **102** (78%). Treatment of acrylate **102** with potassium carbonate in methanol resulted in sequential acetate hydrolysis and intramolecular hetero-Michael addition to give tetrahydropyran **24** (88%). Oxidation of the alcohol **24**, using PCC, then gave aldehyde **103** (51%) which was immediately reacted with methylmagnesium chloride. Oxidation of the resulting mixture of diastereoisomeric diols **104** (77%), again using PCC, finally gave the target compound **13** in 51% yield.

The synthetically derived ketone **13** was reacted with vinylmagnesium bromide and in this manner a diastereoisomerically pure allylic alcohol **105** was obtained, albeit in only 50% yield because of the competing formation of the *bis*-vinylated material arising from attack of the Grignard reagent at the C-1 ester moiety. Treatment of the intermediate 3 °-alcohol (the only observed mono-vinylated material) with phosphorous tribromide in ether at 0 °C afforded the rearranged allylic bromide **106** (91%). Reaction of the latter compound with diphenylethoxyphosphine in refluxing THF resulted in a Michaelis-Arbuzov reaction and formation of the phosphine oxide **95** (84%) which was obtained as a crystalline solid.

While the reaction sequence just described proceeds with high levels of diastereo-control, the initial KSAE of nerol (**97**) only proceeds in *ca.* 50 % ee with the result that phosphine oxide **95** is only obtained with the same level of enantiomeric enrichment. However, since compound **95** is a crystalline material the ee can be raised to >98% by repeated recrystallisation although the attendant loss of material is severe.

When the initial synthetic approaches to herboxidiene were undertaken by Bui and Banwell, many of the stereochemical features associated with the target molecule had not

been fully elucidated. In particular, there were ambiguities with respect to the relative stereochemistries at C-12, C-16, C-17 and C-18. Furthermore, the absolute stereochemistry of this compound had not been determined. Nevertheless, extensive efforts to develop an approach to the herboxidiene side chain were undertaken and these led to the construction of the aldehyde **122** by the route shown in Scheme 1.16. The synthesis began with commercially available methyl (*R*)-3-hydroxy-2-methylpropionate **107** which was converted into the corresponding benzyl ether **108** (73%) under conditions which avoid racemisation.[40] Ester **108** was then reduced, by standard methods, to the corresponding alcohol **109** (85%) and this was, in turn, subjected to Swern oxidation to obtain the aldehyde **110** (80%), a molecule notoriously prone to racemisation.[63] Nucleophilic addition of vinylmagnesium bromide to this last compound produced a 1:1 mixture of diastereomeric addition products (70% combined yield) which could be separated from one another by flash chromatography. The more polar material proved to be compound **111** which was subjected to *O*-methylation using potassium hydride and methyl iodide. In this manner the *bis*-ether **112** was obtained in (94%) and immediately subjected to ozonolytic cleavage thereby affording compound **113** (92%). Reaction of aldehyde **113** with methylmagnesium chloride provided a 4:1 mixture of compound **114** and its C-18 epimer (herboxidiene numbering) (96% combined yield) which could only be separated from one another by HPLC techniques. It was more convenient, therefore, to convert this mixture into the corresponding *tert*-butyldimethylsilyl ethers, **115** and 18-*epi*-**115** (93% combined yield) and these were then hydrogenolysed to give the corresponding mixture of alcohols **116** and 18-*epi*-**116** (97% combined yield) that could be readily separated by flash chromatography. Oxidation of alcohol **116** with the Swern reagent provided the corresponding aldehyde **117** which was then reacted with isopropenyl cuprate[15,50] to give allylic alcohol **118** (83%) as the only detectable product of reaction. For the purposes of unequivocal characterisation, compound **118** was desilylated and the structure of the resulting crystalline diol was determined by single-crystal X-ray anlysis.

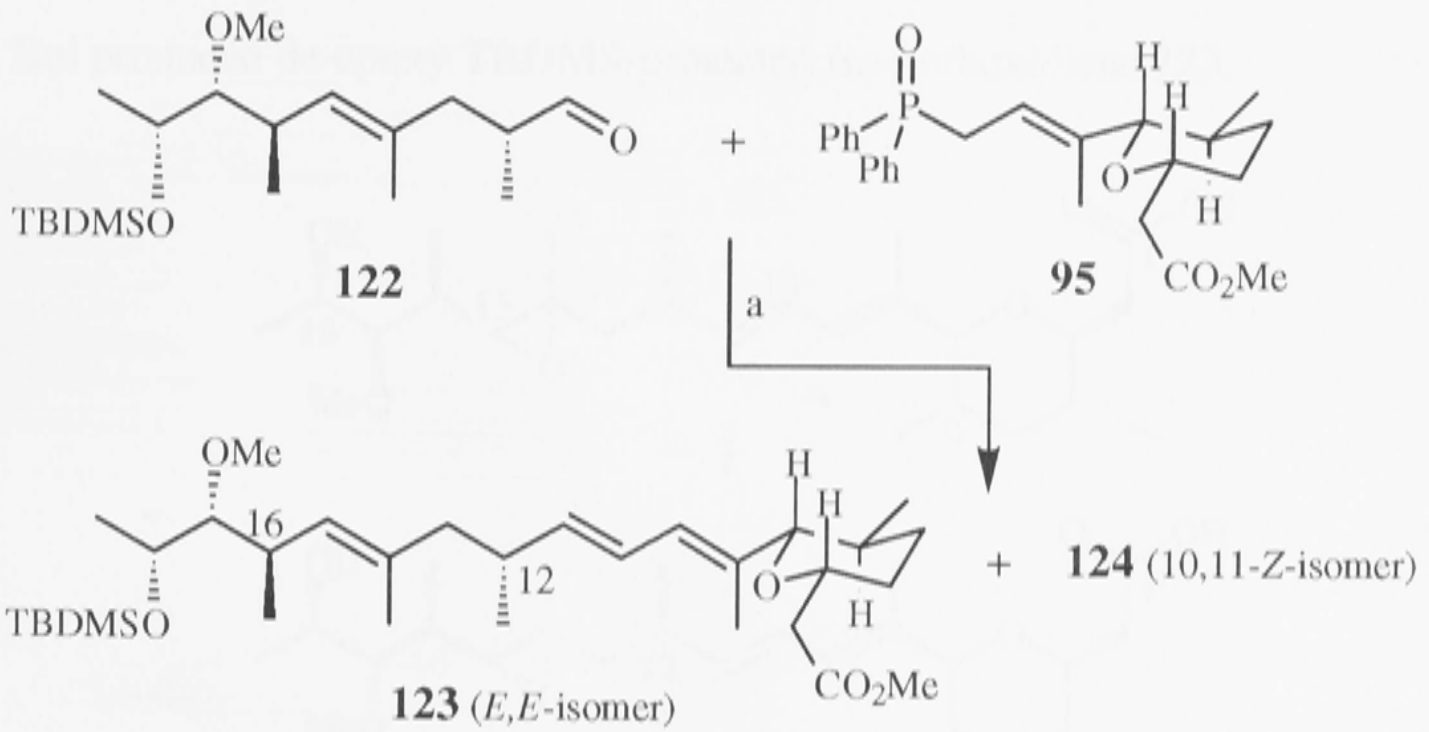


Scheme 1.16: Bui's Synthesis of an Isomer, **122**, of the Herboxidiene Side Chain.

Reagents and conditions: (a) $BnOC(NH)CCl_3$, CF_3SO_3H (cat.)/CH_2Cl_2, 0 to 18 °C; (b) $LiAlH_4/Et_2O$, 0-5 °C; (c) Me_2SO, $Cl(CO)_2Cl/CH_2Cl_2$, -60 °C then NEt_3; (d) $CH_2=C(H)MgBr$/THF, 0 °C; (e) MeI, KH/THF, 0 to 18 °C; (f) O_3/CH_2Cl_2, -78 °C then Me_2S; (g) MeMgCl/THF, -78 °C; (h) TBDMSCl, imidazole/DMF, 60 °C; (i) H_2 (1 atm), 10% Pd on C/EtOH, rt; (j) Me_2SO, $Cl(CO)_2Cl/CH_2Cl_2$, -60 °C then NEt_3; (k) $H_2C=C(Me)Br$, *t*-BuLi, CuBr.DMS/Et_2O, -78 °C; (l) $(EtCO)_2O$, DMAP, pyridine, rt; (m) $KN(TMS)_2$/THF, then TMSCl-Et_3N, HMPA then heat at 45 °C; (n) $LiAlH_4/Et_2O$, 0 °C; (o) Me_2SO, $Cl(CO)_2Cl/CH_2Cl_2$, -60 °C then NEt_3.

Completion of the synthesis of the aldehyde **122** involved conversion of alcohol **118** into the corresponding propionate **119** (82%) which was, in turn, subjected to an Ireland-Claisen rearrangement[50] by sequential treatment with KHMDS and TMSCl-NEt_3 then heating the resulting (*Z*)-silyl ketene acetal at 45 °C. In this manner the γ, δ-unsaturated carboxylic acid **120** (80%) was obtained. Reduction of the acid **120** to the corresponding alcohol **121** (83%) was achieved with $LiAlH_4$ and the latter compound was then oxidised to the required aldehyde **122** (94%) using the Swern reagent.

Bui connected the side chain aldehyde **122** to the core fragment **95** using a WHE-type condensation and obtained a 4:1 mixture of the (*E*,*E*) and (*E*,*Z*)-dienes, **123**, **124** respectively, in a combined yield of 70 % (Scheme 1.17). The major product, **123**, could be purified by HPLC and the spectroscopic data obtained on this material were in accord with the assigned structure. Unfortunately, Bui did not have enough time or material to selectively epoxidise compound **123** so as to generate the corresponding herboxidiene methyl ester analogue.

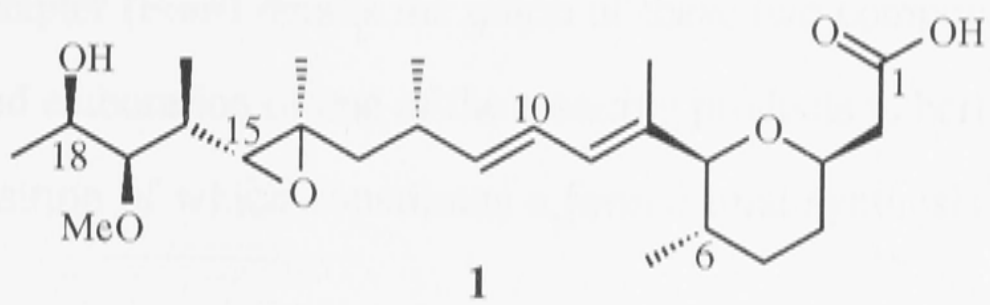


Scheme 1.17: Chin Bui's Synthesis of De-epoxy TBDMS-protected *iso*-Herboxidiene **123**.

Reagents and conditions: (a) NaH/THF, 18 °C to 60 °C then CH_2N_2/Et_2O, -20 °C.

While Bui's work represents a ground breaking effort to assemble herboxidiene-like compounds there are some significant drawbacks to his methodology that require attention before a useful synthesis of target **1** can be attained. The first deficiency of the Bui's work is associated with construction of the core phosphine oxide **95** since this pivotal molecule is only obtained in *ca* 50% ee because of the low levels of enantioselectivity associated with the initial Katsuki-Sharpless asymmetric epoxidation (KSAE) of nerol. The second major deficiency derives from the lack of diastereo-control associated with many of the steps involved in assembling of the side chain molecule **122** as well as the fact that this compound does not have the required stereochemistry at C-12 and C-16 for incorporation into herboxidiene itself.

At the time initial studies (both here and overseas) directed toward the total synthesis of herboxidiene were commenced neither the complete relative nor absolute stereochemistries of herboxidiene were known. Hence, Kocienski's earlier work culminated in the preparation of herboxidiene A **39**, a diastereoisomer of **1** differing from the natural product at C-12, C-17 and C-18.[8] In parallel work, in these laboratories Chinh Bui produced de-epoxy TBDMS-protected *iso*-herboxidiene **123**.



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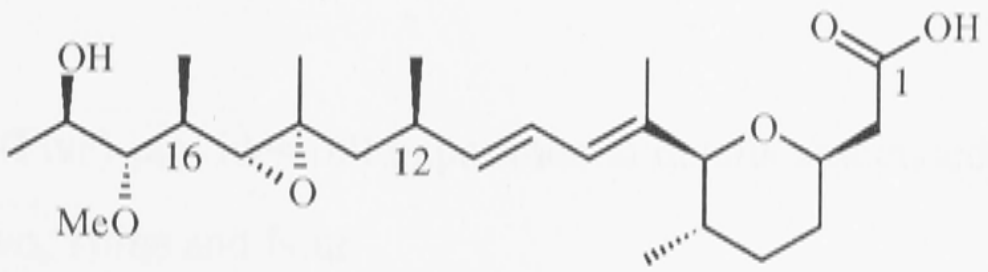

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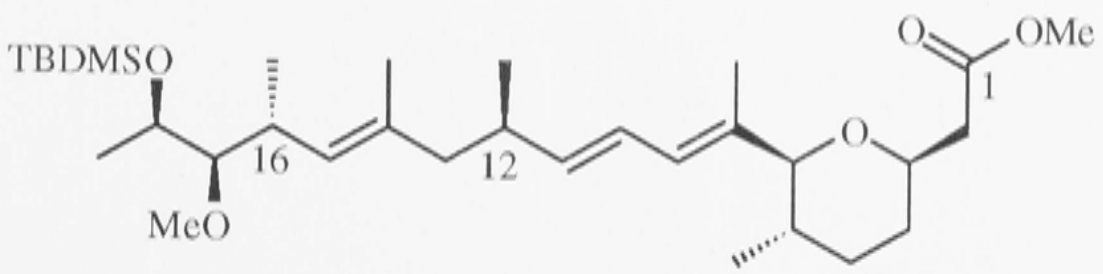
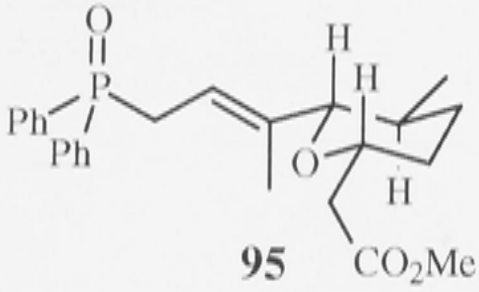


123

It is against this background that the work described in this thesis was undertaken. The primary objective was the development of an enantio- and diastereo-selective total synthesis of herboxidiene proper. This could be contemplated as a realistic objective because at the time of commencement of this project Edmunds *et al* had finally established the full stereo-structure of the target molecule **1** (see pages 7-12).

The objectives of the work described in this thesis, then, were to address the above-mentioned deficiencies in the Bui work and, thereby, achieve a diastereo- and enantio-selective total synthesis of herboxidiene. The research detailed in the following chapter (Chapter Two) was directed toward the development of a highly enantio-selective synthesis of phosphine oxide **95**, while the research described in Chapter Three has culminated in construction of the side chain aldehyde 12-*epi*-**94**.



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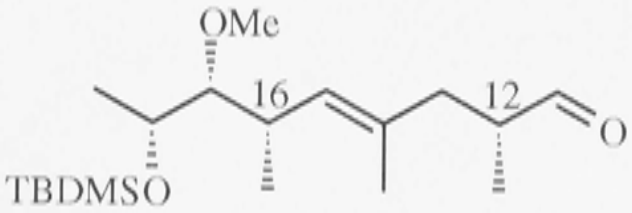


12-*epi*-**94**

The penultimate Chapter (Four) details the union of these two compounds *via* Horner-Wittig chemistry and elaboration of one of the resulting products to herboxidiene methyl ester (**5**), the acquisition of which constitutes a formal total synthesis of herboxidiene itself.

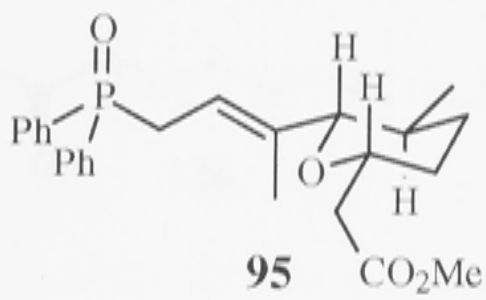
The Final Chapter (Five) provides full experimental details associated with the claims made in Chapter Two, Three and Four.

CHAPTER TWO

Enantio- and Diastereo-selective Synthesis of the Herboxidiene Core Molecule 95

2.1 Preparation and Katsuki-Sharpless Asymmetric Epoxidation of Allylic Alcohol 127. Formation of Epoxy-alcohol 128

As noted in the introduction, the initial objective of the work described herein was to establish a highly enantioselective route to the pivotal herboxidiene core molecule **95**. The pivotal step was to involve asymmetric epoxidation of an appropriate allylic alcohol so a brief commentary on this type of oxidation reaction is now provided.



95

The asymmetric epoxidation of allylic alcohols using *t*-butyl hydroperoxide in the presence of titanium tetraisopropoxide and a chiral dialkyl tartrate is now described as the Katsuki-Sharpless asymmetric epoxidation (KSAE) reaction and this process follows a pathway that frequently allows for high optical induction (>90% ee).[24] The major two advantages of this enantioselective oxidation reaction are (i) the reaction gives uniformly high asymmetric induction for a wide range of primary allylic alcohols and (ii) the reaction proceeds in a highly predictable fashion in terms of which enantiomeric form of the product is obtained (Figure 2.1).

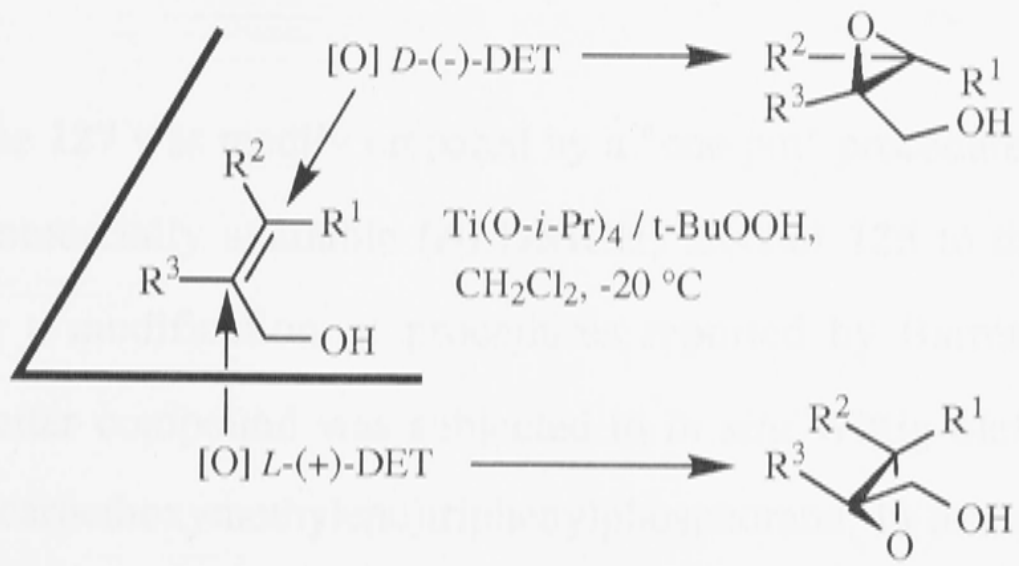
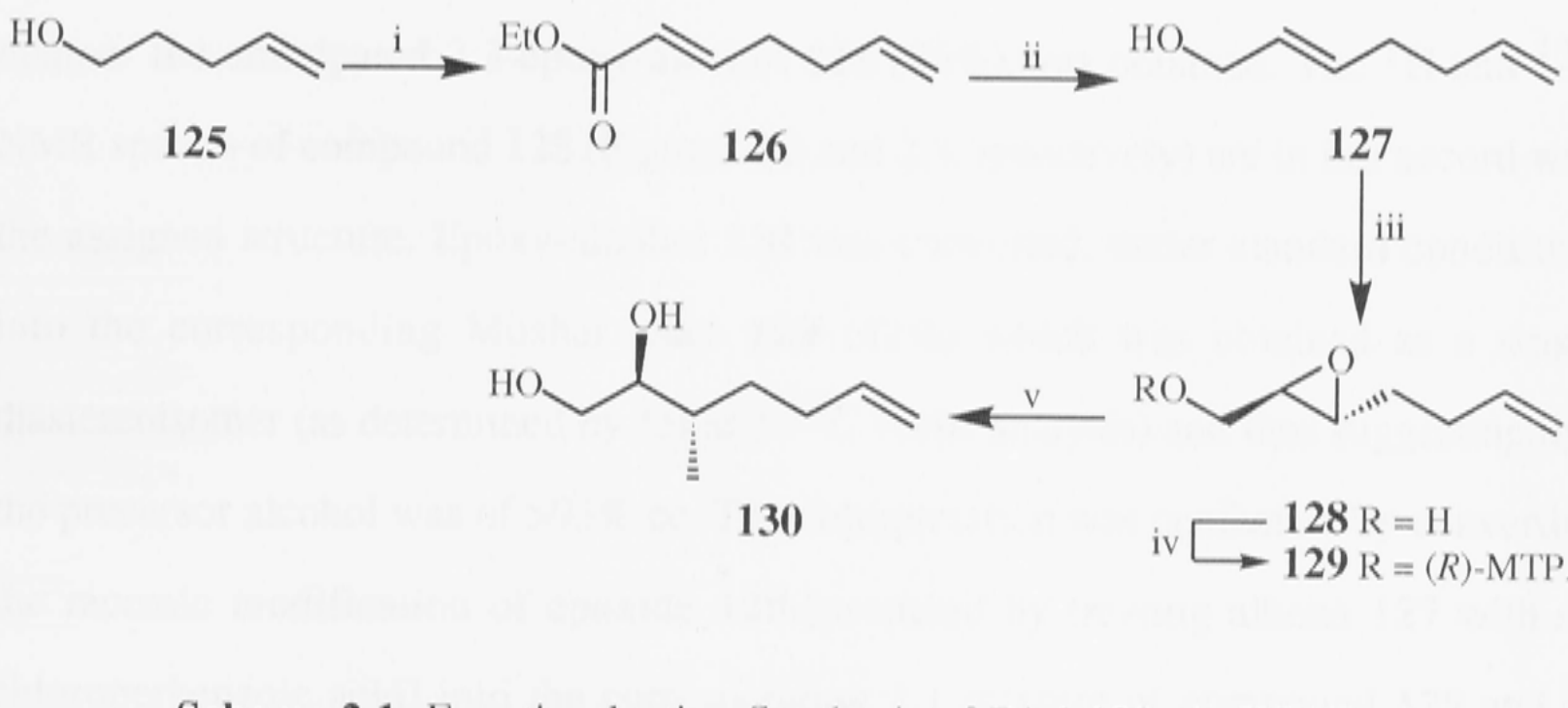


Figure 2.1: Nmenonic Used in Determining the Absolute Stereochemistry of the Epoxidation Product Derived from KSAE of Allylic Alcohols.

In contrast to the situation with (*Z*)-1,2,2,-trisubstituted alkenes (e.g. nerol), the KSAE of allylic alcohols proceeds in high ee when (*E*)-1,2-disubstituted alkenes are employed as substrates.[24] Consequently, the allylic alcohol **127** (Scheme 2.1) was chosen as the substrate for KSAE on the basis that the product epoxide **128** would be obtained in high ee. In addition, it was anticipated that nucleophilic methylation of the latter compound could be achieved in both a regio- and diastereo-selective manner so as to produce diol **130** containing the methyl group required at C-6 (herboxidiene numbering) in the target molecule **95**.



Scheme 2.1: Enantioselective Synthesis of Diol **130** *via* KSAE of Allylic Alcohol **127**.

Reagents and Conditions: (i) Swern oxidation then $Ph_3P{=}C(H)CO_2Et/CH_2Cl_2$, 2 h; (ii) DIBAL-H/ CH_2Cl_2, 2 h, -78 °C; (iii) KSAE, diethyl *D*-(-)-tartrate/CH_2Cl_2; (iv) DMAP, NEt_3/CH_2Cl_2 then **127** and Mosher chloride; (v) Me_3Al/CH_2Cl_2, 0 °C to rt, 10 h.

The pivotal alkene **127** was readily prepared by a "one-pot" procedure involving initial oxidation of commercially available (ALDRICH) alcohol **125** to the corresponding aldehyde. Using a modification of procedures reported by Barrett,[25] Lee [26] and Taylor,[27] this latter compound was subjected to *in situ* Wittig olefination with the stabilised ylide (carbethoxymethylene)triphenylphosphorane. In this manner the α, β-unsaturated ester **126**[26,28] (98%) was obtained and the illustrated (*E*)-configuration about the Δ^2-double-bond was established from the magnitude of the vicinal spin-spin

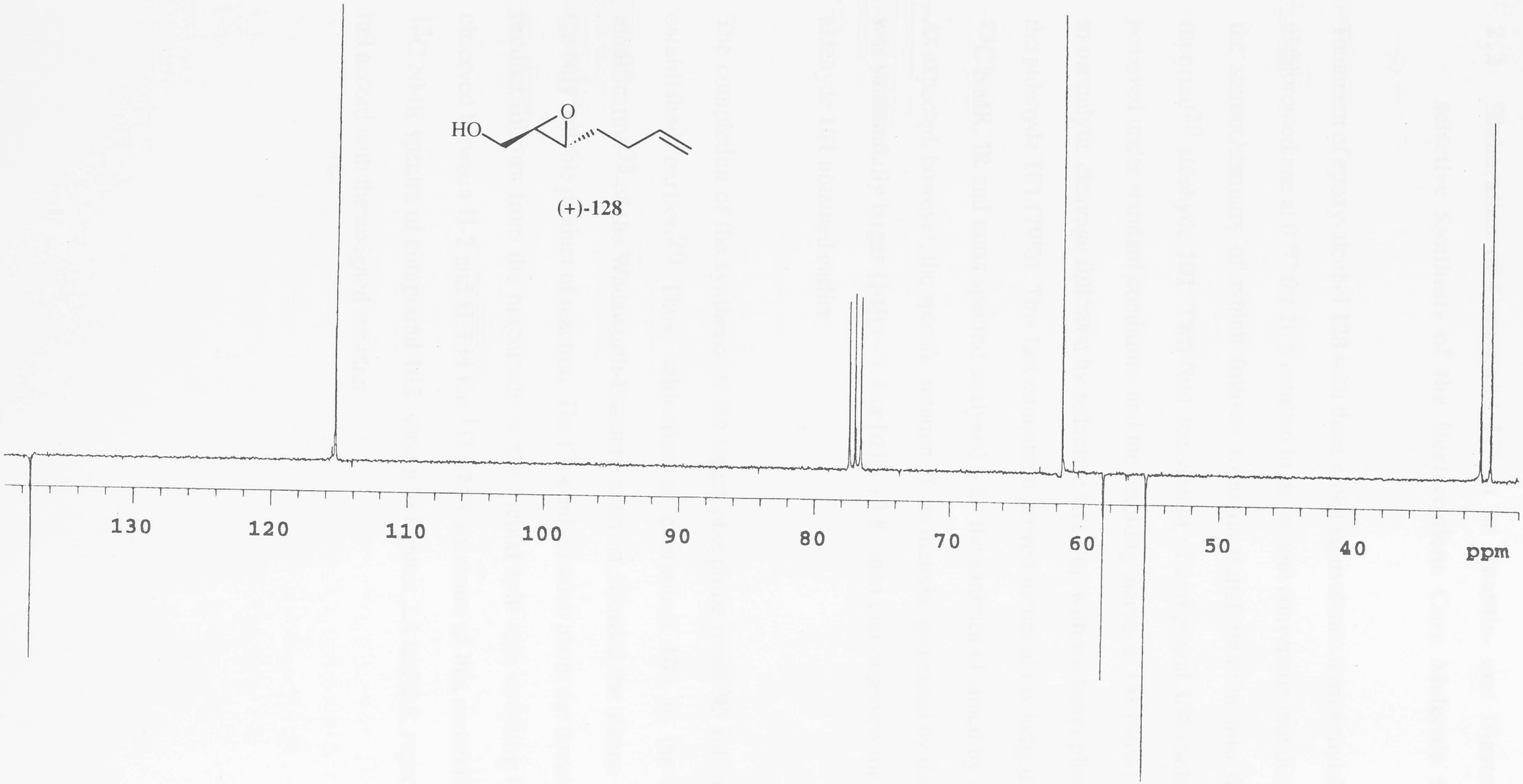
coupling (J = 15.6 Hz) observed between H-2 and H-3 in the ^{1}H NMR spectrum of this material. This sequential "one-pot" oxidation-aldehyde olefination procedure is of great synthetic value[29] as the intermediate aldehyde is difficult to handle due to its high volatility and odoriferous nature.

DIBAL-promoted 1,2-reduction of compound **126** proceeded smoothly to give the target alcohol **127**[26,30] in 85% yield, and the various spectral data derived from this material were in full accord with the assigned structure. KSAE of compound **127** was effected under standard conditions using catalytic quantities of diethyl *D*-(-)-tartrate and in this manner the anticipated 2,3-epoxy-alcohol **128** (70%) was obtained. The ^{1}H and ^{13}C NMR spectra of compound **128** (Figures 2.2 and 2.3, repectively) are in full accord with the assigned structure. Epoxy-alcohol **128** was converted, under standard conditions, into the corresponding Mosher ester **129** (42%) which was obtained as a single diastereoisomer (as determined by ^{1}H and ^{13}C NMR analysis) and thus suggesting that the precursor alcohol was of >95% ee. This interpretation was confirmed by converting the racemic modification of epoxide **128** [prepared by treating alkene **127** with *m*-chloroperbenzoic acid] into the corresponding 1:1 mixture of compound **129** and its diastereo-isomer and observing that these Mosher esters were readily differentiated from one another by 300 MHz ^{1}H NMR spectrometry (see Experimental Section). The assignment of the absolute configuration of epoxide **128** was based, in the first instance, on applying the nmenonic shown in Figure 2.1 and this was subsequently confirmed by its conversion into the previously reported tetrahydropyran **13**, the degradation product obtained from herboxidiene.

(+)-128

Figure 2.2: 300 MHz ^{1}H NMR Spectrum of 2,3-Epoxy-alcohol (+)-**128**.

(Spectrum recorded in $CDCl_3$ solution)



(+)-128

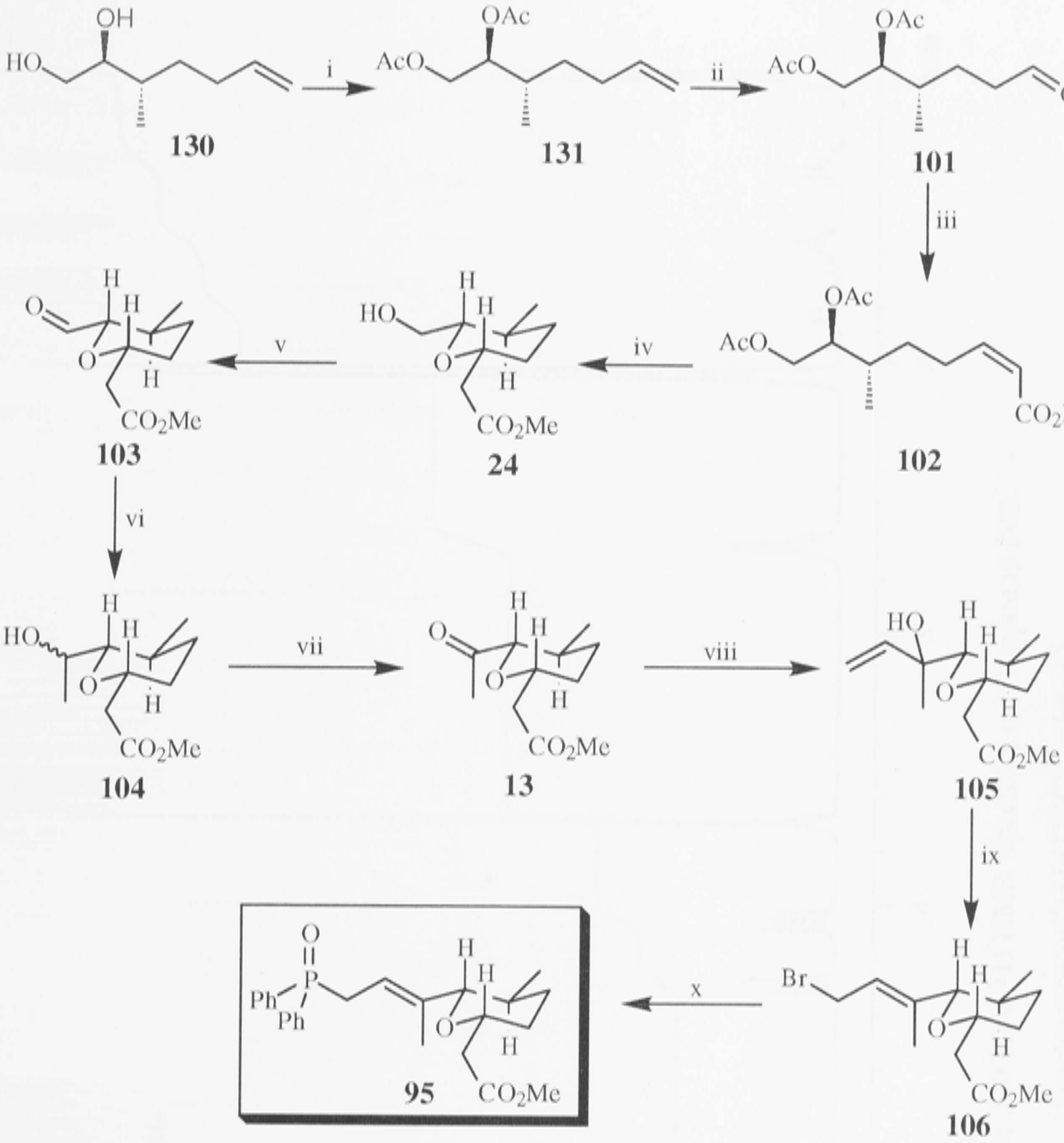
Figure 2.3: 75.5 MHz APT ^{13}C NMR Spectrum of 2,3-Epoxy-alcohol (+)-**128**.

(Spectrum recorded in $CDCl_3$ solution)

2.2 Elaboration of Compound 128 in an Enantio- and Diastereo-selective Synthesis of the Herboxidiene Core Molecule 95

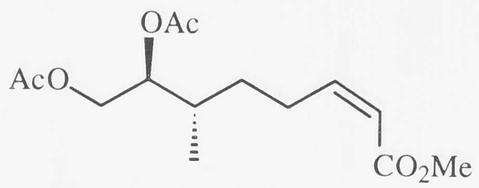
Treatment of epoxy-alcohol **128** with three molar equivalents of trimethylaluminium[32] in dichloromethane at 0 °C for 10 h resulted in its smooth conversion into diol **130** (83%)[10] the stereochemistry of which follows from its transformation into the previously reported[20] aldehyde **101**. Two-fold acetylation of compound **130** (Scheme 2.2) was achieved under standard conditions and the resulting diacetate **131** (96%) was subjected to ozonolytic cleavage followed by reductive work-up with triphenyl phosphine to give the aldehyde **101** (79%). This last compound proved identical (as judged by ^{1}H NMR, ^{13}C NMR, IR and mass spectral analysis) with the samples obtained by Bui's route.[20] As expected, however, the specific rotation of the material generated by the present route was substantially larger {$[\alpha]_D$ +7.3 *vs* $[\alpha]_D$ +3.8} than that observed for the sample of aldehyde **101** obtained earlier.

The completion of the synthesis of the target phosphine oxide **95** followed the route established earlier.[20] Thus, subjection of compound **101** to the Still-Gennari modification[33] of the Wadsworth-Emmons reaction afforded the alkene **102** (80%) as the only isolable product of reaction. The (*Z*)-configuration about the double-bond in this product follows from the magnitude of the vicinal spin-spin coupling (J = 11.5 Hz) observed between H-2 and H-3 in the ^{1}H NMR spectrum of this material. The ^{1}H and ^{13}C NMR spectra of compound **102** (shown in Figures 2.4 and 2.5, repectively) are in full accord with the assigned structure.



Scheme 2.2: Completion of the Enantio- and Diastereo-selective Route to the Herboxidiene Core Molecule **95**.

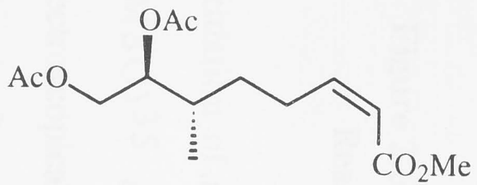
Reagents and Conditions: (i) Ac_2O, DMAP(trace)/pyridine, 18 °C, 3 h; (ii) O_3/CH_2Cl_2 then PPh_3; (iii) $MeO_2CCH_2P(O)(OCH_2CF_3)_2$, 18-crown-6/$CH_3CN$-complex, $KN(TMS)_2$/THF, -78 °C; (iv) K_2CO_3/MeOH, rt, then MeOH, H_2SO_4 (trace), rt; (v) pyridine.SO_3 complex/DMSO, CH_2Cl_2, 0 °C; (vi) MeMgCl/THF, -78 °C to 0 °C; (vii) Dess-Martin periodinane/CH_2Cl_2, rt, 1 h; (viii) $H_2C{=}C(H)MgBr$/THF, -78 °C; (ix) PBr_3/Et_2O, 0 °C; (x) Ph_2POEt/THF, reflux, 2 h.



102

Figure 2.4: 300 MHz ^{1}H NMR Spectrum of Compound **102**.

(Spectrum recorded in $CDCl_3$ solution)



102

Figure 2.5: 75.5 MHz APT ^{13}C NMR Spectrum of Compound **102**.

(Spectrum recorded in $CDCl_3$ solution)

Treatment of compound **102** with potassium carbonate in methanol resulted in removal of the acetate groups and a subsequent intramolecular hetero-Michael addition reaction to give the tetrahydropyranyl acetic acid ester **24** along with varying quantities of the corresponding acid. As a consequence, the crude reaction mixture was treated with acidic methanol and in this manner compound **24** was obtained in 71% yield. The C-3 epimer of compound **24** was not detected in the reaction mixture and it is believed, on the basis of model studies,[34] that the (*Z*)-geometry about the double bond in substrate **102** exerts a controlling influence in ensuring, at least under conditions of kinetic control, a *cis*-relationship between the anomeric substituents in the cyclisation product. Thus, the conversion **102→24** is believed to involve a transition state structure such as that depicted in Figure 2.6 wherein chelation of the participating metal ion (K^+) by two partially negatively charged oxygens can only take place because of the (*Z*)-geometry about the double bond.

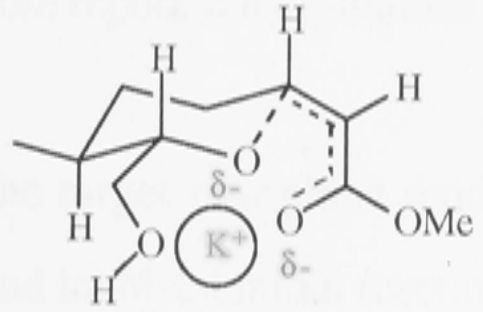


Figure 2.6: Plausible Transition State Structure Associated with the Cyclisation Reaction Leading to Tetrahydropyranylacetic Acid Methyl Ester **24**.

Oxidation of alcohol **24** under Parikh-Doering conditions (pyridine-SO_3 activated DMSO)[35] afforded the corresponding aldehyde **103** (60%) which proved spectroscopically identical with the sample obtained by Bui's earlier route. In addition, the optical rotation of this material matched that reported by Edmunds for enantiomerically pure material.[5] After considerable experimentation with a range of nucleophilic methylating agents, methylmagnesium chloride proved to be the most effective in adding to the aldehydic moiety associated with compound **103**. The resulting mixture of distereoisomeric 2°-alcohols (35%) was immediately oxidised to the corresponding

methyl ketone **13** (48%) using the Dess-Martin periodinane.[36] The optical rotation of this compound matched that reported for a sample obtained by ozonolytic cleavage of herboxidiene itself (Table 2.1).

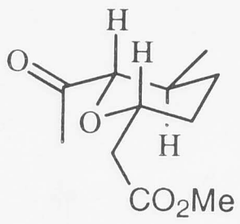
Table 2.1: Comparison of the Specific Rotations of Compounds **13**, **24** and **103** Prepared in the Course of the Present Work with Literature Values.

Compound	Specific Rotation[a]	Literature Value[5]
13	-91 (1.2)	-95 (1.5)
24	+9.8 (1.0)	+9.4
103	-65 (0.45)	-62 (0.5)

a Specific rotations were determined at 22 °C. Values in parenthesis refer to sample concentrations in g/100 mL of $CHCl_3$ (spectroscopic grade). See Experimental Section for details.

The ^1H and ^{13}C NMR spectral data obtained on compound **13**, (see Figures 2.7 and 2.8) matched, in all respects, those reported by Edmunds and co-workers.

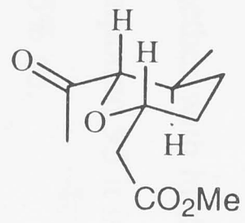
Elaboration of ketone **13** to the target phosphine oxide **95** followed the previously established procedures of Bui and involved initial reaction of the former compound with vinyl magnesium bromide. This resulted in generation of the desired mixture of diastereoisomeric 3°-alcohols albeit in only 60 % yield because of the formation of by-products deriving from competing nucleophilic addition to the ester moiety. Treatment of the intermediate 3°-alcohols with phosphorous tribromide, in ether at 0 °C,[18] then afforded the allylic bromide **106** (91%), which engaged in a Michaelis-Arbuzov reaction with diphenylethoxyphosphine[27,38] to deliver, after chromatographic purification, compound **95** (84%) as a crystalline solid.



13

Figure 2.7: 300 MHz ^{1}H NMR Spectrum of Compound **13**.

(Spectrum recorded in $CDCl_3$ solution)



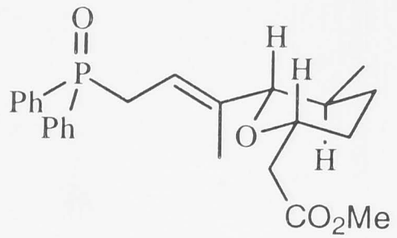
13

Figure 2.8: 75.5 MHz APT ^{13}C NMR Spectrum of Compound **13**.

(Spectrum recorded in $CDCl_3$ solution)

Extensive but nevertheless conventional spectroscopic characterisation of compound **95** allowed for confident assignment of its structure. In the ^{1}H NMR spectrum (Figure 2.9) the ten-proton envelope centred at δ 7.62 was assigned to the protons of the two phenyl groups. The olefinic proton, H-9 (herboxidiene numbering), resonated as a multiplet at δ 5.50 due to, *inter alia*, allylic coupling to the C-8 methyl group protons. Interestingly, in the ^{13}C NMR spectrum (Figure 2.10) the resonance due to C-10 appeared as a doublet at δ 30.7 with $J\ ^{13}C\text{-}^{31}P = 70$ Hz. The ^{31}P NMR spectrum showed a single peak at δ 31.0. The mass spectrum exhibited a strong molecular ion at *m/z* 426 (51%) and the fragment ion at *m/z* 395 derives from the loss of the OCH_3 radical. The IR spectrum showed absorption bands at 1736 and 1180 cm^{-1} corresponding to the carbonyl (C=O) and phosphine oxide (P=O) groups, respectively. In addition, satisfactory high resolution mass spectra was obtained for compound **95**. Finally, the melting point of this compound (m.p. 125-126 °C) matched that reported earlier for multiply recrystallised material.[20]

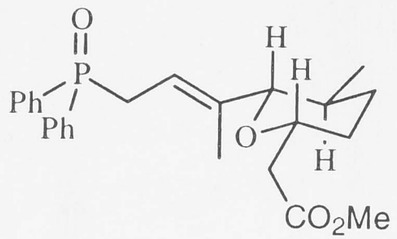
The specific rotation of compound **95** produced by the route just described was much lower {$[\alpha]_D$ -0.4 *vs* $[\alpha]_D$ -32.8} than that measured for the material generated by Bui's original route. Fortunately a sample of compound **95** derived by this earlier sequence was still available and a re-determination of the specific rotation resulted in a value identical to that observed for the newly prepared sample. Consequently it was concluded that Bui's earlier determination of optical rotation for compound **95** is in error. In addition, given the absence of any racemisation pathways in the synthetic sequence just described together with high levels of enantioselectivity obtained in the KSAE reaction leading to compound **95** it is reasonable to conclude that phosphine oxide **95** has been obtained in >95% ee.



95

Figure 2.9: 300 MHz ^{1}H NMR Spectrum of Phosphine Oxide **95**.

(Spectrum recorded in $CDCl_3$ solution)



95

Figure 2.10: 75.5 MHz APT ^{13}C NMR Spectrum of Phosphine Oxide **95**.

(Spectrum recorded in $CDCl_3$ solution)

CHAPTER THREE

Enantio- and Diastereo-selective Synthesis of the Herboxidiene Side Chain Molecule 94

3.1 Synthesis of the C-16 to C-19 Fragment of the Herboxidiene From Commercially Available Hydroxy-ester 96

The synthetic route that was employed in order to achieve a highly diastereo-selective synthesis of the side chain **94** (Figure 3.1) associated with herboxidiene is shown in Scheme 3.1. It begins with methyl (*S*)-3-hydroxy-2-methylpropionate **96** which is produced in large quantities *via* microbial oxidation of isobutyric acid[62] and which is commercially available (e.g. ex SIGMA) in optically pure form (>99% ee). It was anticipated that C-2 of this synthon would become C-16 of the herboxidiene side chain (Figure 3.1) and this single "purchased" centre of chirality would be employed to control all of the other stereogenic centres associated with the side chain of target **1**. Initial work (Scheme 3.1) was directed toward elaborating the ester moiety within substrate **96** so as to install C-17 to C-19 while subsequent elaboration of the hydroxyl group within the same starting material would be used for installation of C-14 to C-12 so as to ultimately produce the target side chain molecule **94**.

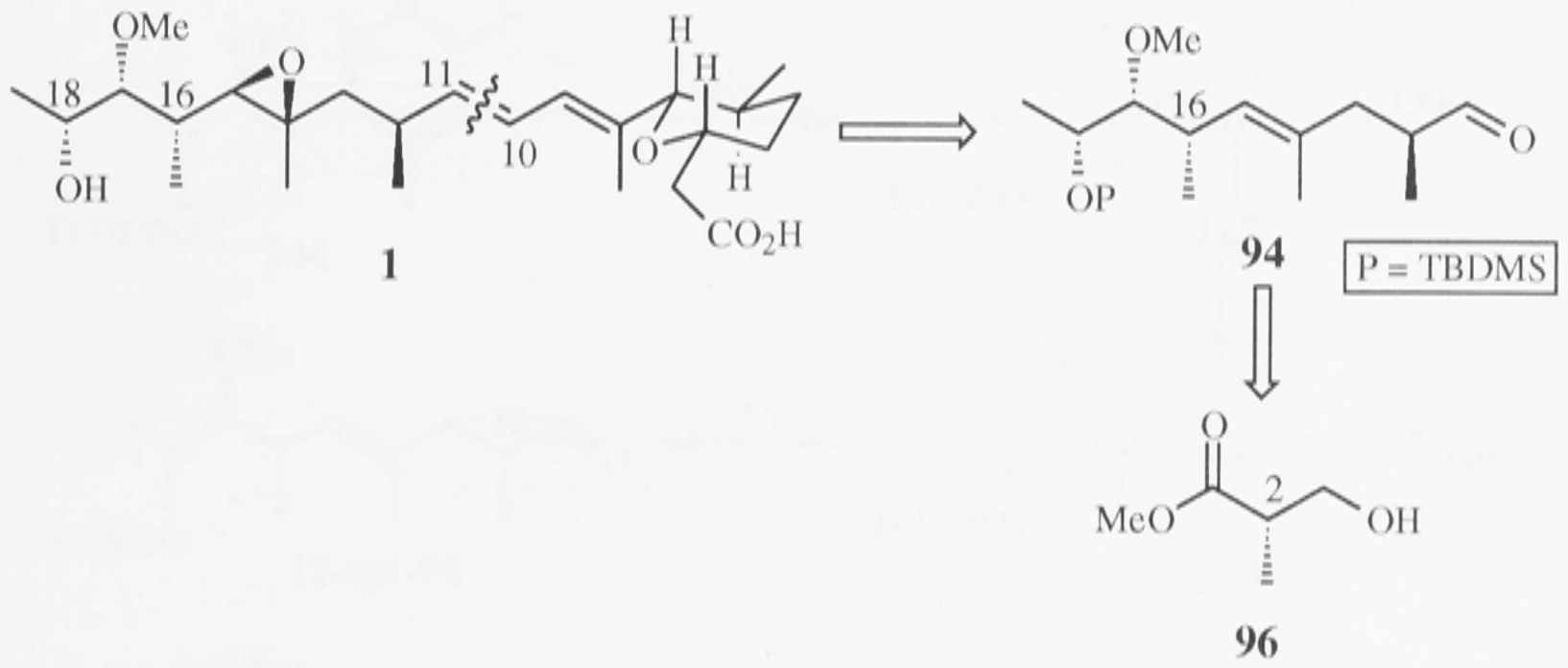
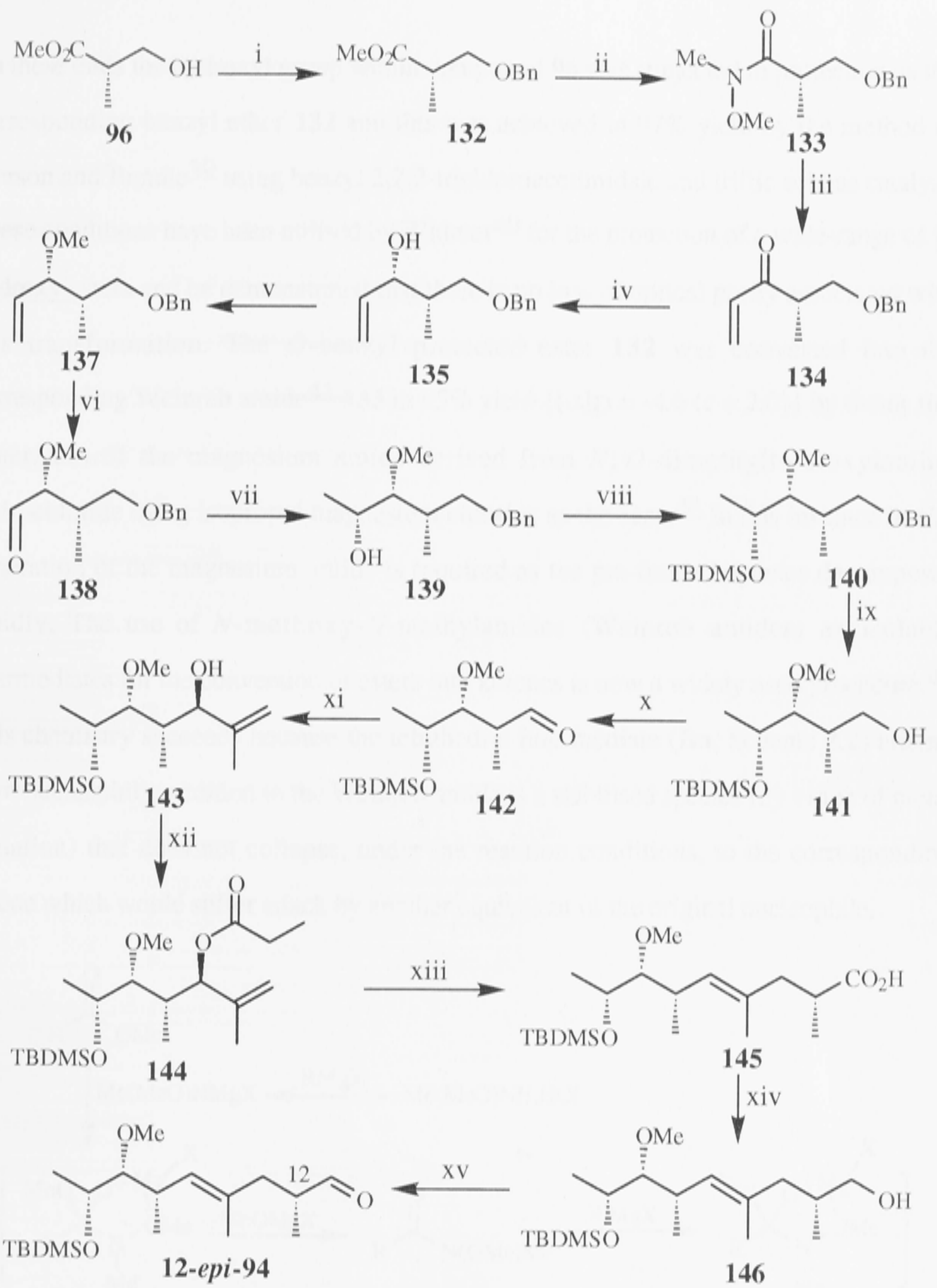


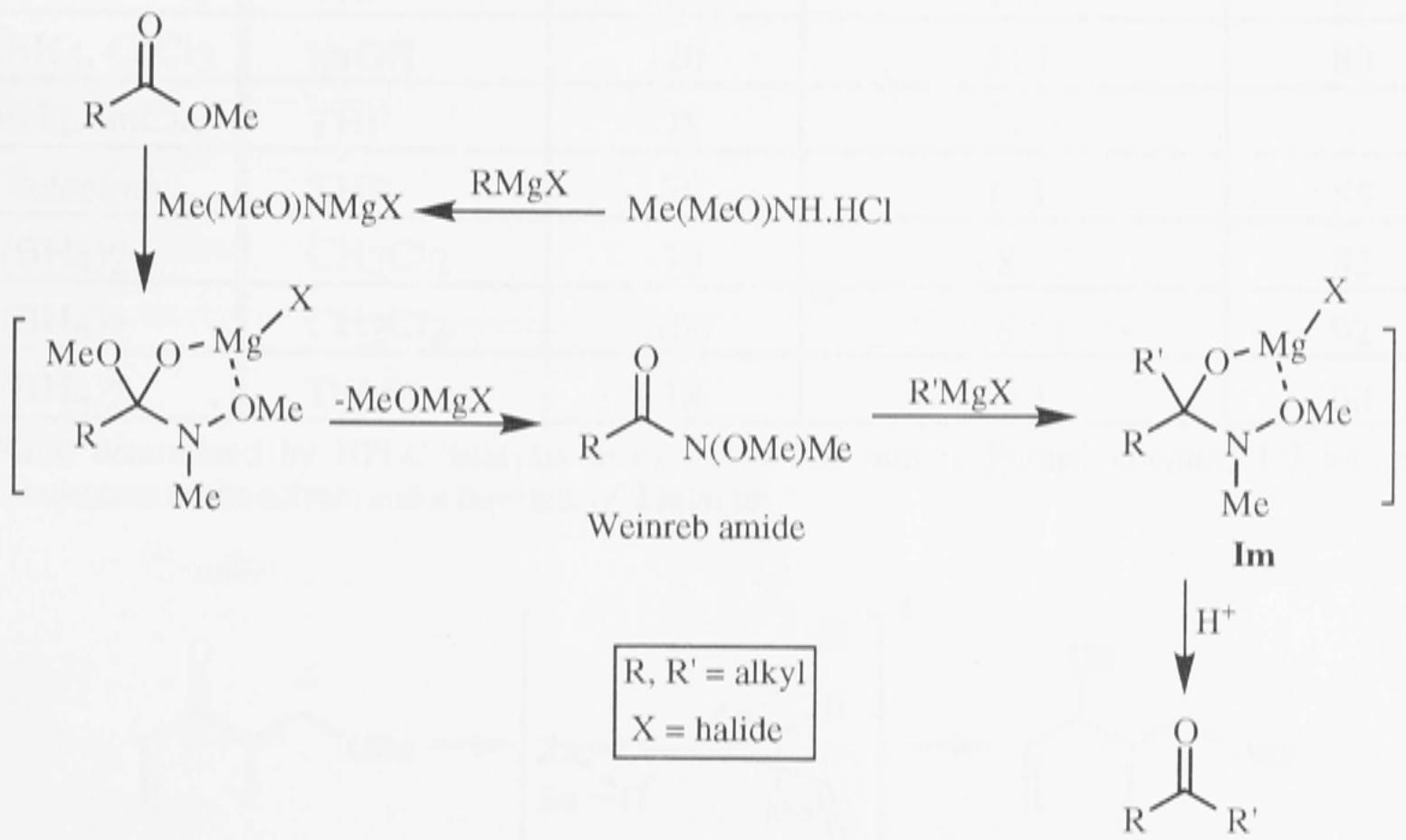
Figure 3.1: Retrosynthetic Relationships between Herboxidiene (**1**), the Side Chain Molecule **94** and the Side Chain Synthon **96**.



Scheme 3.1: Diastereoselective Synthesis of Herboxidiene Side Chain Synthon 12-*epi*-**94**.

Reagents and conditions: (i) $BnOC(NH)CCl_3$, CF_3SO_3H (cat.)/CH_2Cl_2, 0 to 18 °C; (ii) Me(MeO)NH.HCl, *i*-PrMgCl/THF, -15 °C; (iii) $H_2C{=}C(H)MgBr$/THF, 0 °C; (iv) $Zn(BH_4)_2/CH_2Cl_2$, -78 °C; (v) MeI, KH/THF, 0 to 18 °C; (vi) O_3/CH_2Cl_2, -78 °C then Me_2S; (vii) Me_2Zn, $TiCl_4/CH_2Cl_2$, -78 °C; (viii) TBDMSCl, imidazole/DMF, 60 °C; (ix) H_2 (1 atm), $Pd(OH)_2$ on C/ THF, rt; (x) SO_3.pyridine complex/DMSO, CH_2Cl_2, rt; (xi) $H_2C{=}C(Me)Br$, *t*-BuLi, CuBr.DMS/Et_2O, -78 °C; (xii) $(EtCO)_2O$, DMAP, pyridine, rt; (xiii) LDA, HMPA/THF, TBDMSCl, -78 °C to 50 °C; (xiv) $LiAlH_4/Et_2O$, 0 °C; (xv) Dess-Martin periodinane/CH_2Cl_2, rt.

To these ends the hydroxyl group within compound **96** was subjected to protection as the corresponding benzyl ether **132** and this was achieved in 97% yield by the method of Iverson and Bundle[39] using benzyl 2,2,2-trichloroacetimidate and triflic acid as catalyst. These conditions have been utilised by Widmer[40] for the protection of a wide-range of β-hydroxy esters and he demonstrated that there is no loss of optical purity associated with this transformation. The *O*-benzyl protected ester **132** was converted into the corresponding Weinreb amide[41] **133** in 95% yield {$[\alpha]_D$ = -4.6 (c = 2.0)} by the *in situ* generation of the magnesium amide derived from *N*, *O*-dimethylhydroxylamine hydrochloride using isopropyl magnesium chloride as the base.[42] In this instance *in situ* generation of the magnesium amide is required as the pre-formed species decomposes rapidly. The use of *N*-methoxy-*N*-methylamides (Weinreb amides) as isolable intermediates for the conversion of esters into ketones is now a widely used procedure.[43] This chemistry succeeds because the tetrahedral intermediate (**Im**, Scheme 3.2) arising from nucleophilic addition to the Weinreb amide is a stabilised species (by virtue of metal chelation) that does not collapse, under the reaction conditions, to the corresponding ketone which would suffer attack by another equivalent of the original nucleophile.



Scheme 3.2: Conversion of an Ester to a Ketone Through Controlled Nucleophilic Addition to an Intermediate Weinreb Amide.

Reaction of vinylmagnesium bromide with the Weinreb amide **133** gave the α-chiral ketone **134** in 92% yield[43] and this latter compound was subsequently reduced to the *syn*-alcohol **135**. To achieve this reduction diastereoselectively, a range of reducing agents was investigated (Table 3.1). The best diastereoselectivities (>8:1 *syn /anti*) were observed when $Zn(BH_4)_2$ was used and this useful outcome can be explained by the intervention of the effects of 'chelation control'.[44] A possible transition state structure is presented in Figure 3.2 in order to highlight chelation of the zinc metal ion and the Bürgi-Dunitz trajectory associated with hydride ion attack which gives rise to the major product, *viz. syn*-alcohol **135**.

Table 3.1 : Stereoselectivities obtained by Hydride-Type Reduction of Ketone **134** to Alcohols **135** and **136**.

Reducing agent	Solvent	Temp °C	Ratio of Alcohols* 135:136	Combined yield (%)
DIBAL	CH_2Cl_2	-78	1 : 1	77
DIBAL	THF	-78	-	-
DIBAL, $ZnCl_2$	THF	-78	1 : 1	76
DIBAL, $SnCl_4$	THF	-78	1 :1	65
$NaBH_4$, $CeCl_3$	iprOH	-20	2 : 1	80
$LiBH_4$, $SnCl_4$	THF	-78	-	-
K- Selectride	THF	-78	1 :3	55
$Zn(BH_4)_2$	CH_2Cl_2	-78	> 8 : 1	92
$Zn(BH_4)_2$	CH_2Cl_2	-100	> 8 : 1	92
$Zn(BH_4)_2$	TBME	-78	5 : 1	60

* Ratio determined by HPLC analysis using 7.8 x 300 mm μ–Porasil column, 1:9 v/v ethyl acetate:hexane as the solvent and a flow rate of 2 ml/min.

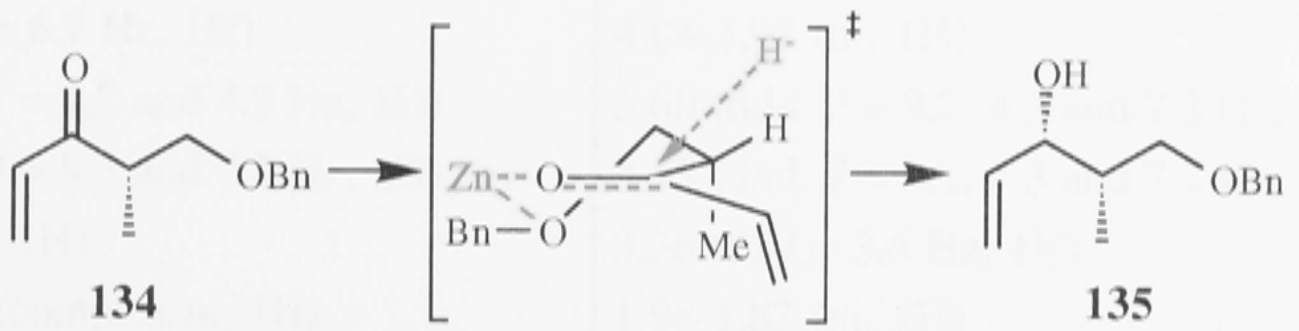


Figure 3.2: Chelation-controlled Reduction of Ketone **134** Leading to Stereoselective Formation of *syn*-Alcohol **135**.

The *syn*- and *anti*-alcohols were readily separated from one another by preparative HPLC techniques and all spectral data obtained on these compounds were in full accord with the data reported for their enantiomeric forms (Tables 3.2, 3.3 and 3.4).[46] The ^{1}H NMR spectra of both the *syn*- and *anti*-alcohols, **135** and **136** respectively, are shown in the Figures 3.3 and 3.4. There are conspicuous differences in the chemical shifts as well as the multiplicities of the protons at C-3, C-4 and C-5 in each of these isomers.

Table 3.2: Comparison of the 300 MHz ^{1}H NMR Spectral Data of the *syn*-Alcohol **135** with Those Reported for its Enantiomer.[a]

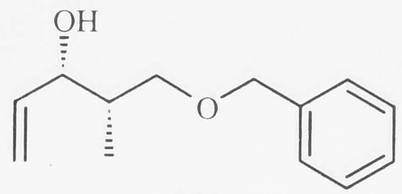
***syn*-Alcohol 135 (δH)**	**Alcohol *ent* - 135 (δH[b])**
7.39-7.28 (complex m, 5H)	7.75-7.25 (m, 5H)
5.88 (ddd, *J*=17.2, 10.6 and 5.4 Hz, 1H)	5.86 (ddd, *J*=17.2, 10.6 and 5.4 Hz, 1H)
5.33-5.16 (complex m, 2H)	5.30-5.14 (m, 2H)
4.51 (s, 2H)	4.49 (s, 2H)
4.28-4.25 (complex m, 1H)	4.27-4.22 (m, 1H)
3.56-3.49 (complex m, 2H)	3.53-3.45 (m, 2H)
3.0 (br.s, 1H)	2.94 (d, *J* = 5.7 Hz, 1H)
2.12-2.05 (complex m, 1H)	2.13-2.00 (m, 1H)
0.91 (d, *J* = 7.0 Hz, 3H)	0.88 (d, *J* = 7.1 Hz, 3H)

[a] All data obtained using $CDCl_3$ as solvent; [b] Data obtained from reference 46.

Table 3.3: Comparison of the 300 MHz ^{1}H NMR Spectral Data Derived from *anti*-Alcohol **136** with Those Reported for its Enantiomer.[a]

***anti*-Alcohol 136 (δH)**	**Alcohol *ent* - 136 (δH[b])**
7.35-7.29 (complex m, 5H)	7.37-7.25 (m, 5H)
5.88 (ddd, *J*=17.2, 10.6 and 5.4 Hz, 1H)	5.83 (ddd, *J*=6.5, 10.4 and 17.2 Hz, 1H)
5.29-5.13 (complex m, 2H)	5.28-5.11 (m, 2H)
4.52 (s, 2H)	4.50 (s, 2H)
4.03 (t, *J* = 6.7 Hz, 1H)	4.04-3.97 (m, 1H)
3.62 (dd, *J* = 9.2 and 4.3 Hz, 1H)	3.60 (ddd, *J* = 9.2 ,4.3 and 7.2 Hz, 1H)
3.47 (dd, *J* = 9.3 and 7.3 Hz, 1H)	3.45 (ddd, *J* = 9.2, 4.3 and 7.2 Hz, 1H)
3.36 (br.s, 1H)	3.36 (d, *J* = 3.6 Hz, 1H)
1.93-1.89 (complex m, 1H)	1.96-1.83 (m, 1H)
0.91 (d, *J* = 7.1 Hz, 3H)	0.90 (d, *J* = 7.0 Hz, 3H)

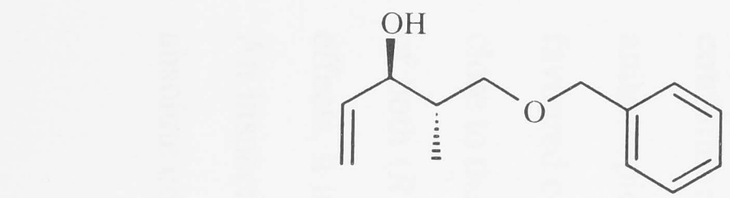
[a] All data obtained using $CDCl_3$ as solvent; [b] Data obtained from reference 46.



135

Figure 3.3: 300 MHz ^{1}H NMR Spectrum of *syn*-Alcohol **135**.

(Spectrum recorded in $CDCl_3$ solution)



136

Figure 3.4: 300 MHz ^{1}H NMR Spectrum of *Anti*-Alcohol **136**.

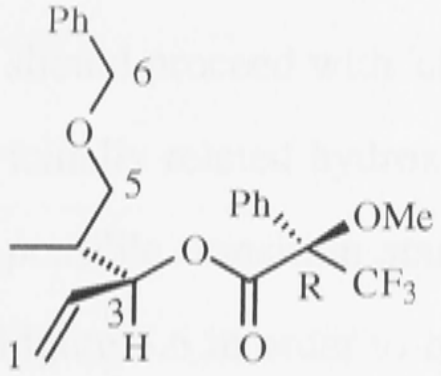
(Spectrum recorded in $CDCl_3$ solution)

Table 3.4: Comparison of the 75 MHz ^{13}C NMR Spectral Data Derived from the *syn*- and *anti*-Alcohols **135** and **136** with those Reported for the Enantiomers.[a]

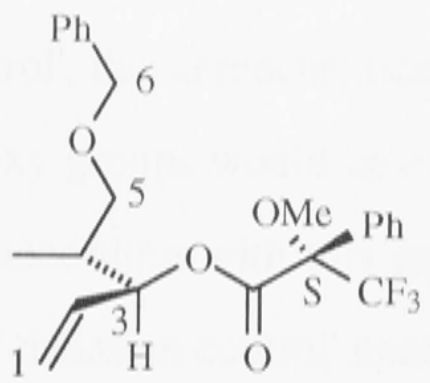
***syn*-Alcohol 135** (δC)	***ent*-135** (δC[b])	***anti*-Alcohol 136** (δC)	***ent*-136** (δC[b])
138.5 (CH)	138.6 (CH)	139.7 (CH)	139.3 (CH)
137.9 (CH_2)	137.9 (CH_2)	138.1 (CH_2)	137.7 (CH_2)
128.3 (CH)	128.3 (CH)	128.7 (CH)	128.2 (CH)
127.6 (2CH)	127.5 (2CH)	128.0 (2CH)	127.5 (2CH)
115.0 (C)	114.9 (C)	116.1 (C)	115.5 (C)
75.0 (CH)	74.8 (CH)	76.9 (CH)	77.0 (CH)
73.6 (CH_2)	73.6 (CH_2)	74.8 (CH_2)	74.1 (CH_2)
73.3 (CH_2)	73.2 (CH_2)	73.7 (CH_2)	73.2 (CH_2)
38.2 (CH)	38.3 (CH)	38.8 (CH)	38.4 (CH)
11.5 (CH_3)	11.4 (CH_3)	14.0 (CH_3)	13.4 (CH_3)

[a] All data obtained using $CDCl_3$ as solvent; [b] Data obtained from reference 46.

The (*S*)- and (*R*)- MTPA ester derivatives of the major reduction product were prepared (by standard methods) in order to confirm the absolute stereochemistry of the newly created secondary alcohol stereocentre within compound **135**. It has been proposed that in deuterated chloroform the MTPA ester derivatives of secondary alcohols exist largely in the conformer such as that shown in Figure 3.5 wherein the trifluoromethyl group eclipses the ester carbonyl which in turn eclipses the methine hydrogen of the secondary alcohol center. For the (*R*)-MTPA ester derivative **147** it can be seen that when this conformer is significantly populated then the phenyl ring is ideally placed to anisotropically shield the benzylic region of the ester derivative. Conversely, the favoured conformer of (*S*)-MTPA ester derivative **148** has the methoxy group residing close to the benzylic region and hence no shielding is expected. By assigning the spectra of both (*R*)- and (*S*)- MTPA ester derivatives and comparing the relative shielding effects, it is possible to confirm the absolute stereochemistry of a secondary alcohol.[47] An inspection of the data in Table 3.5 reveals a shielding pattern consistent with the absolute configurations shown.



147



148

Figure 3.5: (*R*)- and (*S*)- Mosher Ester Derivatives of the *syn*-Alcohol **135**.

Table 3.5: Analysis of the Differences in the Proton Chemical Shifts for Equivalent Protons within Mosher Esters **147** and **148**.

Hydrogen	**δ (*R*)-MTPA (147)**	**δ (*S*)-MTPA (148)**	**Δ [δ (*R*)-δ (*S*)]**
C_1-*trans* H	5.3305	5.2415	+ 0.089
C_1-*cis* H	5.2825	5.232	+ 0.050
C_2-H	5.8371	5.750	+0.087
C_3-H	5.670	5.664	+0.006
C_4-H	2.066	2.111	-0.045
C_5-H	3.2596	3.342	-0.082
C_6-H	4.411	4.466	-0.055
C_4-Me	0.900	0.961	-0.061

Continuing with the synthesis of the target side chain molecule **94**, the HPLC purified *syn*-alcohol **135** was *O*-methylated using methyl iodide and KH and the resulting *bis*-ether **137** was obtained in 85% yield {$[\alpha]_D$ = +12.2 (c = 1.3)}. All spectral data obtained on this latter compound were fully consistent with the gross structure. Most particularly, the ^{1}H NMR spectrum of this material showed a new methoxy methyl resonance at δ 3.27. Compound **137** was subjected to ozonolytic cleavage thereby affording the unstable aldehyde **138** {90%, $[\alpha]_D$ = +22.5 (c = 2.2)} which was immediately reacted with dimethyl zinc in the presence of $TiCl_4$[48] to give the diastereoisomerically pure *syn*-alcohol **139** {70%, $[\alpha]_D$ = +8.6 (c = 2.8)} as the only

isolable reaction product. On the basis that addition of the methyl nucleophile to aldehyde **138** should proceed with 'chelation control', the stereochemical relationship between the vicinally related hydroxy and methoxy groups would be expected to be *syn.*[48, 49] A possible transition state structure according with this general idea is shown in the Figure 3.6 in order to highlight the 'chelation control' exerted by the Ti cation and the trajectory of attack of the methyl nucleophile which result in preferential formation of the *syn*-alcohol **139**.

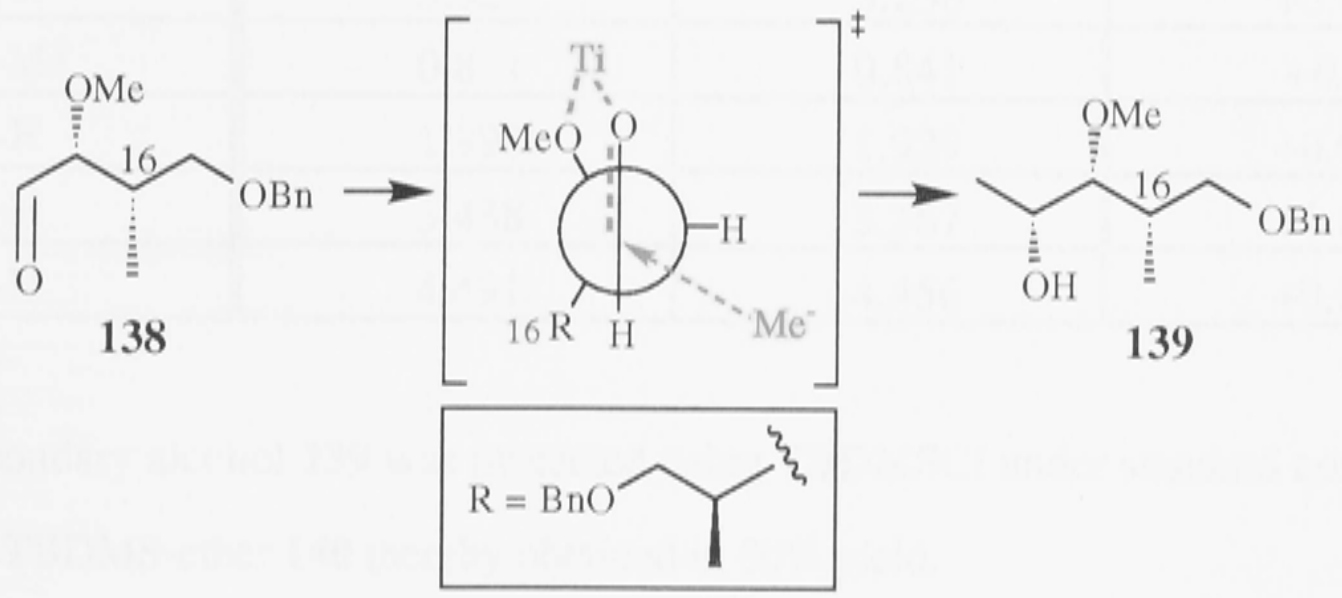
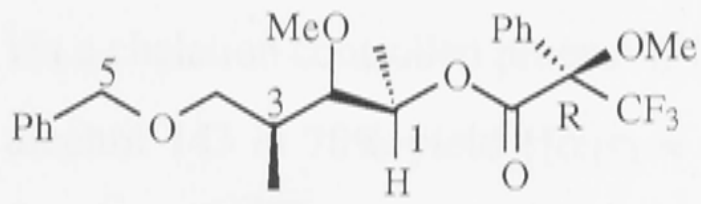
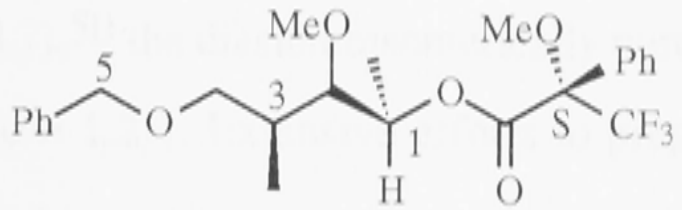


Figure 3.6: Probable Transition State Structure (centre) Associated with the 'Chelation-controlled' Addition of a Methyl Nucleophile to Aldehyde **138**.

Once again, the (*R*)- and (*S*)- MTPA ester derivatives of alcohol **139** were prepared and used to confirm the absolute stereochemistry of the newly created stereogenic centre associated with the secondary alcohol moiety (see Table 3.6).



149



150

Table 3.6: Analysis of the Differences in the Proton Chemical Shifts for Equivalent Protons within Mosher Esters **149** and **150**.

Hydrogen	δ (*R*)-MTPA (**149**)	δ (*S*)-MTPA (**150**)	Δ [δ (*R*)-δ (*S*)]
C_1-Me	1.232	1.293	-0.061
C_1-H	5.169	5.198	-0.029
C_2-OMe	3.307	3.050	+0.257
C_2-H	3.323	3.256	+0.067
C_3-Me	0.871	0.841	+0.03
C_3-H	1.990	1.929	+0.061
C_4-H	3.438	3.367	+0.071
C_5-H	4.491	4.456	+0.035

The secondary alcohol **139** was protected using TBDMSCl under standard conditions and the TBDMS-ether **140** thereby obtained in 80% yield.

With the acquisition of compound **140** the left-hand half (C-15 to C-19) of the side chain had been constructed. To complete the synthesis of target **94**, this fragment now needed to be extended to the right. To these ends compound **140** was subjected to hydrogenolytic debenzylation using Pearlman's catalyst [$Pd(OH)_2$ on carbon] and the ensuing 1°-alcohol **141**, which was obtained in 80% yield, immediately oxidised to the corresponding β-methoxy-aldehyde **142** using the Parikh-Doering reagent.[35] Reaction of compound **142** with the Gilman reagent derived from 2-bromopropene then gave, *via* a chelation controlled process (Figure 3.7),[50] the diastereoisomerically pure allylic alcohol **143** in 70% yield {$[\alpha]_D$ = +3.2 (c = 1.2)}. Extensive efforts to prepare the Mosher ester derivatives of this allylic alcohol (and thereby confirm the stereochemistry at C-15) were not successful perhaps because of unfavourable steric interactions caused by the folding of this compound. Despite this difficulty, the stereochemistry at C-15 could be deduced *via* chemical correlation studies as described later in this chapter as well as in the following one.

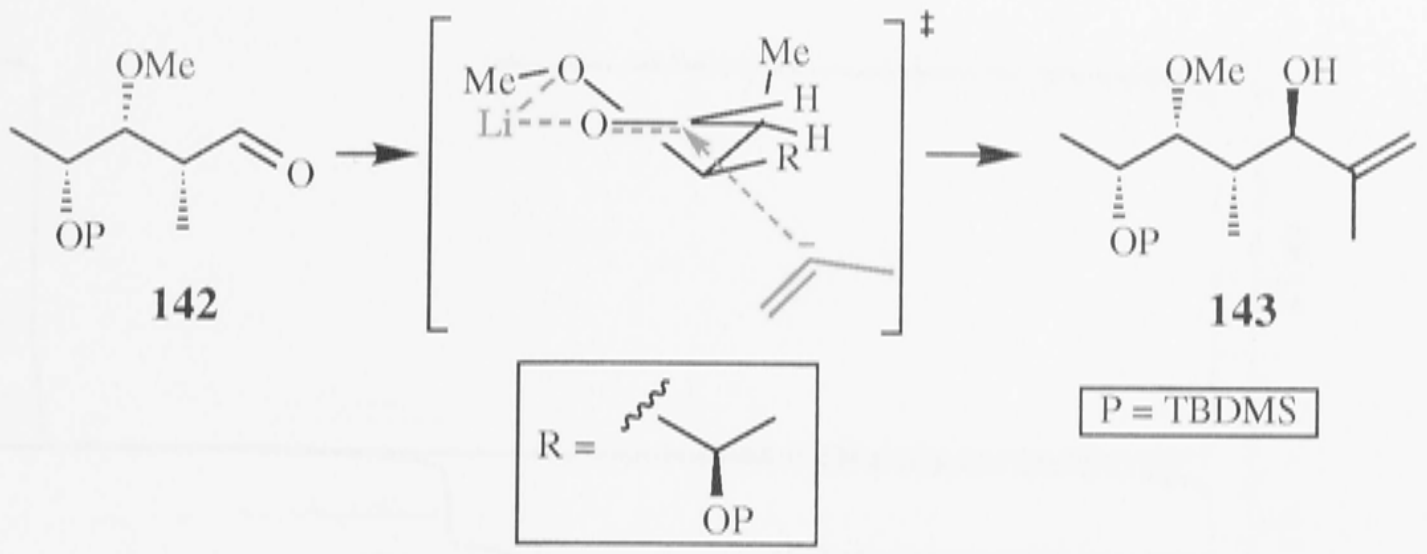
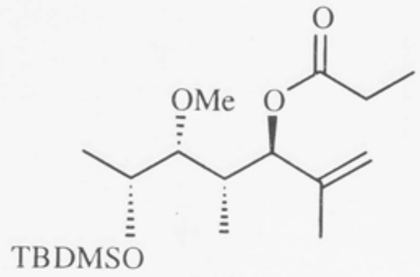


Figure 3.7: Probable Transition State Structure (centre) Associated with the Diastereocontrolled Isopropenylation of Aldehyde **142** to give Alcohol **143**.

3.2 Ireland-Claisen Rearrangement of the Propionate Ester 144: Formation of the C-11 to C-19 Fragment 145

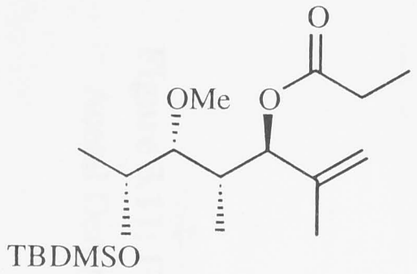
The allylic alcohol with the putative stereostructure **143** was treated with propionic anhydride in pyridine in the presence of DMAP as a catalyst and in this manner the propionate ester **144** was obtained in 90% yield {$[\alpha]_D$ = -22.0 (c = 1.6)}. The derived ^1H and ^{13}C NMR spectra are shown in Figures 3.8 and 3.9, respectively. Compound **144** was subjected to an Ireland-Claisen rearrangement[14,50] involving sequential treatment with LDA then TBDMSCl in HMPA/THF from -78 to 50 °C. The (12*R*)-stereochemistry and the (*E*)-geometry about the double-bond in the ensuing γ,δ-unsaturated carboxylic acid **145** (75%) {$[\alpha]_D$ = +5.8 (c = 2.2)} were initially proposed on the basis of the well-defined outcomes associated with the Ireland-Claisen rearrangements of related substrates (see Figure 3.10) under the same reaction conditions. The probable transition state structure associated with the pivotal rearrangement is shown in Figure 3.11.



144

Figure 3.8: 300 MHz ^{1}H NMR Spectrum of Compound **144**.

(Spectrum recorded in $CDCl_3$ solution)



144

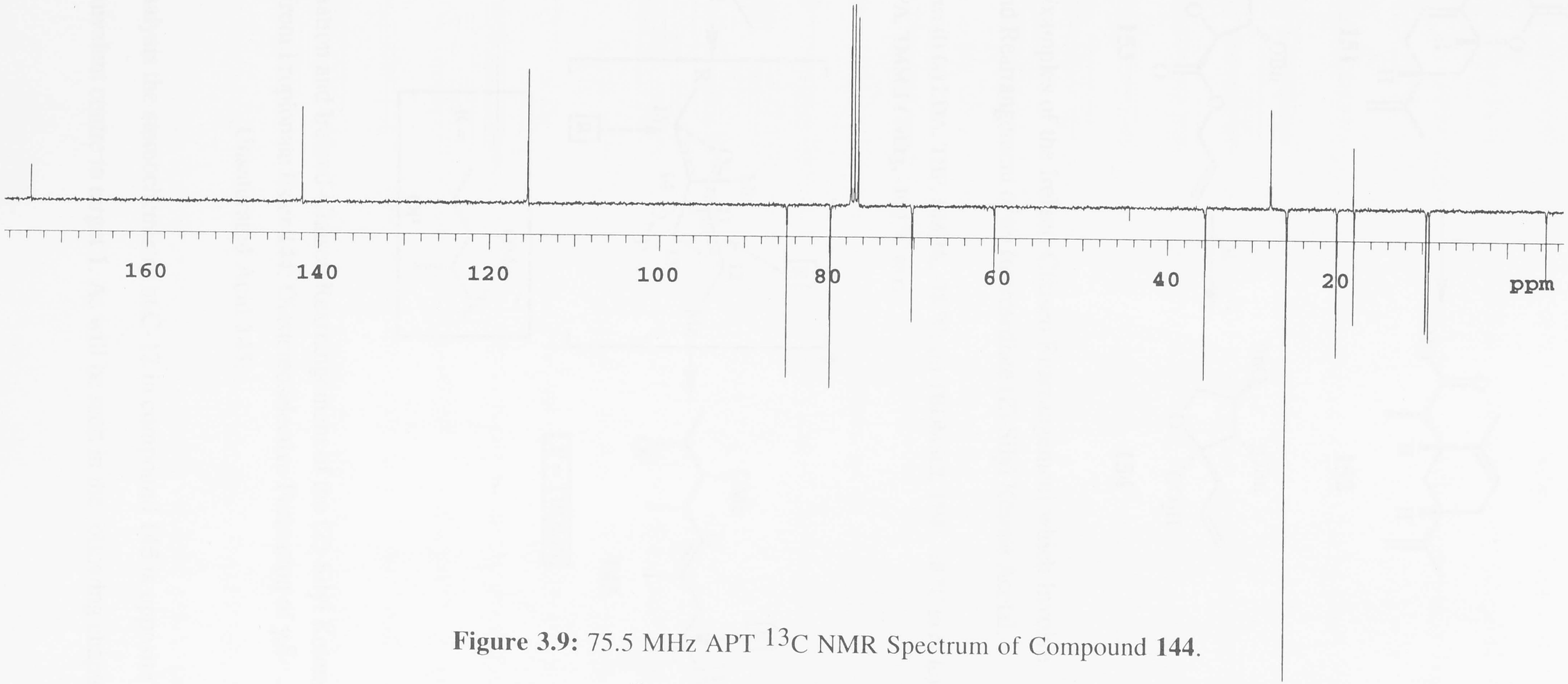


Figure 3.9: 75.5 MHz APT ^{13}C NMR Spectrum of Compound **144**.

(Spectrum recorded in $CDCl_3$ solution)

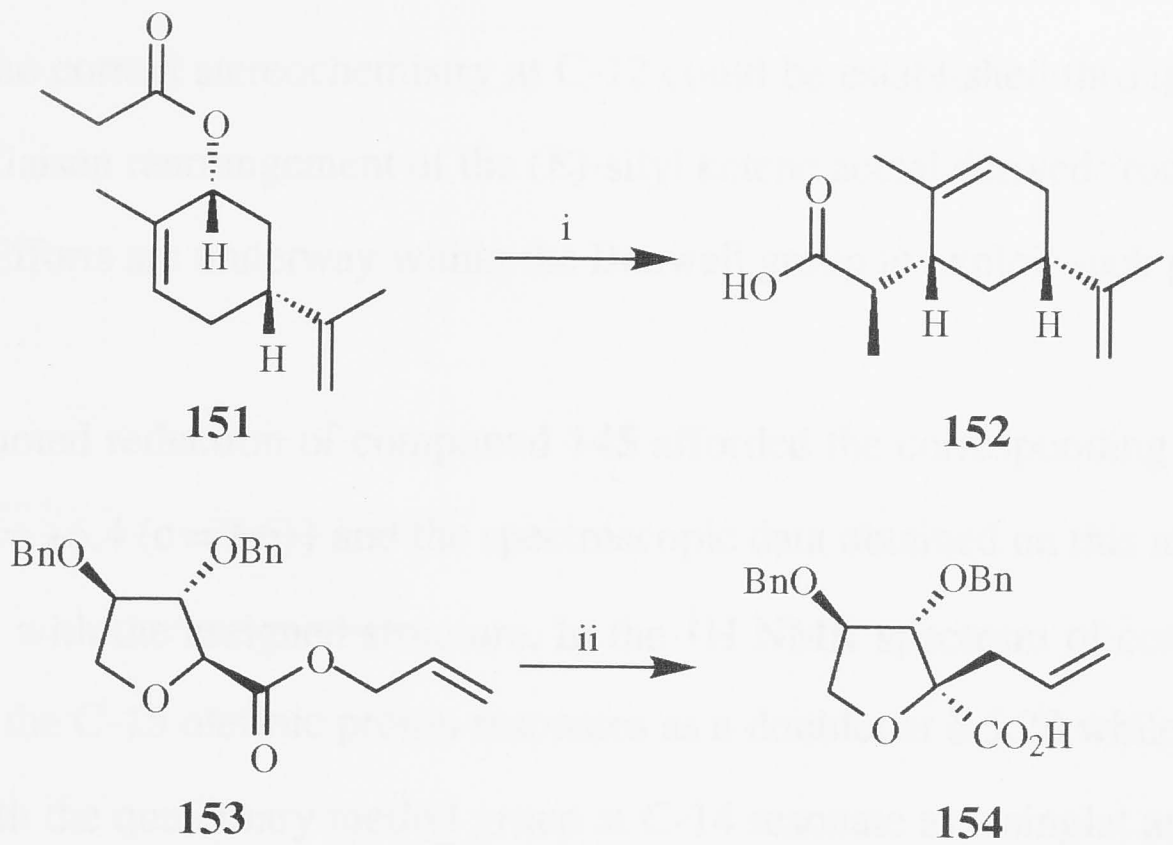


Figure 3.10: Examples of the Ireland-Claisen Rearrangement which Involve Formation and Rearrangement of an Intermediate (Z)-Silyl Ketene Acetal.

Reagents and conditions: (i) (a) LDA, THF, HMPA, -78 °C; (b) TBDMSCl, THF, -78 °C to rt; (c) 50 °C, 6h; (ii) LDA, HMPA, TMSCl / NEt_3, -100 °C to rt.

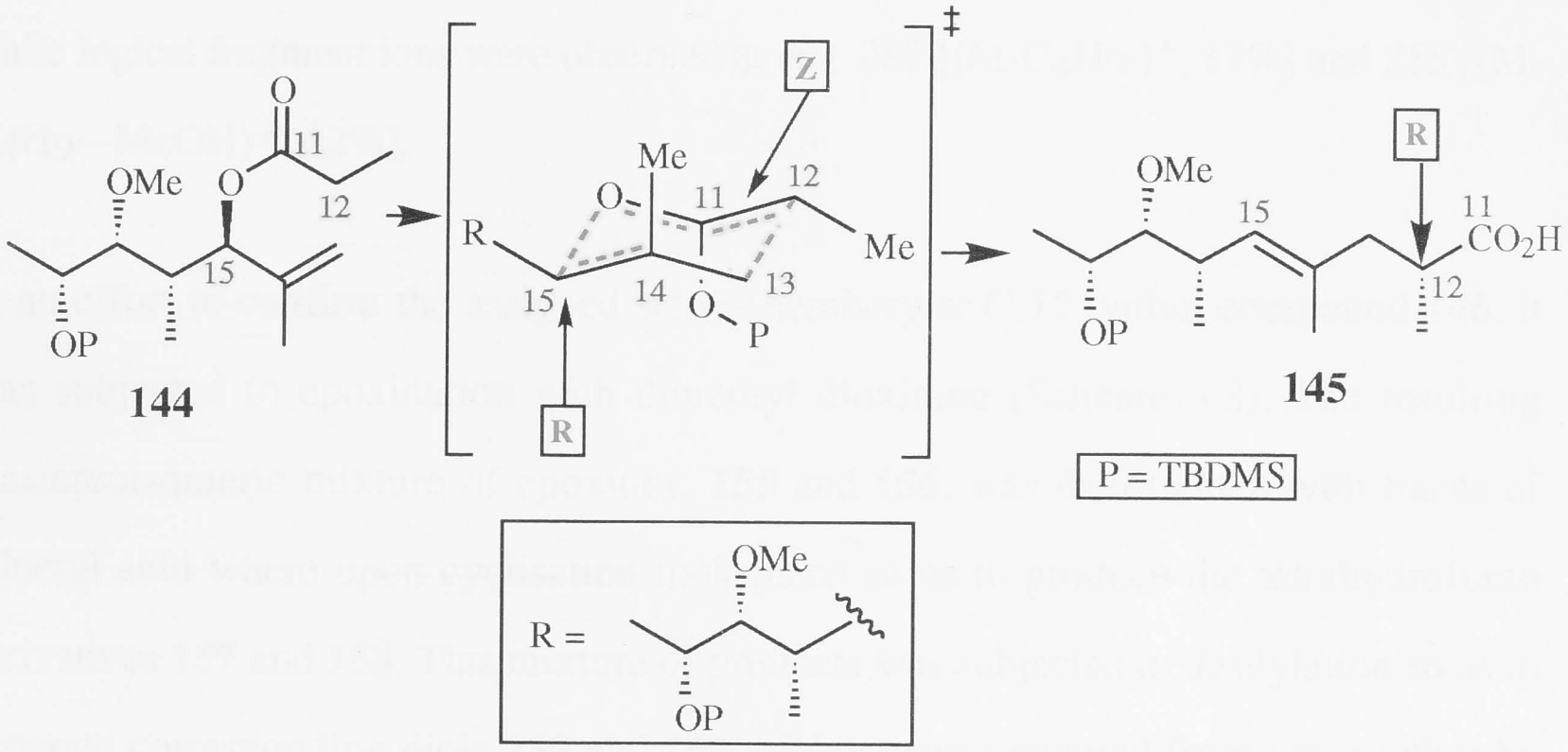


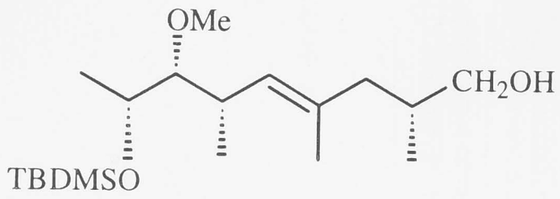
Figure 3.11: Formation and Ireland-Claisen Rearrangement of the (Z)-Silyl Ketene Acetal Derived from Propionate Ester **144**: Diastereoselective Formation of γ,δ-Unsaturated Acid **145**.

On the basis of this analysis the stereochemistry at C-12 in compound **145** is opposite to that required at the equivalent centre in target **1**. As will be seen in the following chapter,

this "stereochemical error" can be corrected (*via* an epimerisation process) but in the longer term the correct stereochemistry at C-12 could be established through formation and Ireland-Claisen rearrangement of the (*E*)-silyl ketene acetal derived from propionate ester **144**.[53] Efforts are underway within the Banwell group to exploit such possibilities.

$LiAlH_4$-promoted reduction of compound **145** afforded the corresponding alcohol **146** (80%) {$[\alpha]_D$ = +6.4 (c = 1.6)} and the spectroscopic data obtained on this material were in full accord with the assigned structure. In the ^1H NMR spectrum of compound **146** (Figure 3.12) the C-15 olefinic proton resonates as a doublet at δ 5.20 while the protons associated with the quaternary methyl group at C-14 resonate as a singlet at δ 1.62. The three doublets in the downfield region correspond to the protons associated with the three secondary methyl groups. The ^{13}C NMR spectrum (Figure 3.13) displayed the expected seventeen resonances, the diagnostic ones being at δ 132.0 and δ 130.8 which correspond to the olefinic carbons at C-15 and C-14, respectively. The 70 eV electron impact mass spectrum of compound **146** exhibited a molecular ion at *m/z* 344 (9%), while logical fragment ions were observed at *m/z* 287 [$(M-C_4H_9\cdot)^+$, 17%] and 255 [$(M-C_4H_9\cdot -MeOH)^+$, 12%].

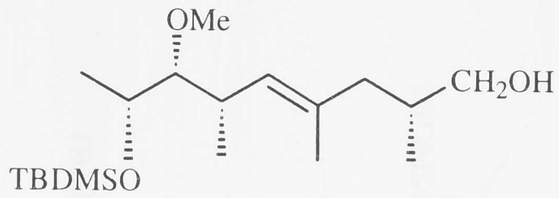
In an effort to confirm the assigned stereochemistry at C-12 within compound **146**, it was subjected to epoxidation with dimethyl dioxirane (Scheme 3.3). The resulting diastereoisomeric mixture of epoxides, **155** and **156**, was then treated with traces of mineral acid where-upon cyclisation took place so as to produce the tetrahydrofuran derivatives **157** and **158**. This mixture of products was subjected to desilylation so as to generate corresponding diols **159** and **160**, which were separated from one another by HPLC techniques. Spectroscopic analysis of these compounds clearly indicated that they were structurally related to but stereochemically distinct from the diol **12** obtained during the degradation studies carried out by Edmunds *et al* on herboxidiene.[5] These results are taken as confirmation of the proposal (*vide infra*) that the carboxylic acid **145** arising



146

Figure 3.12: 300 MHz ^{1}H NMR Spectrum of Compound **146**.

(Spectrum recorded in $CDCl_3$ solution)

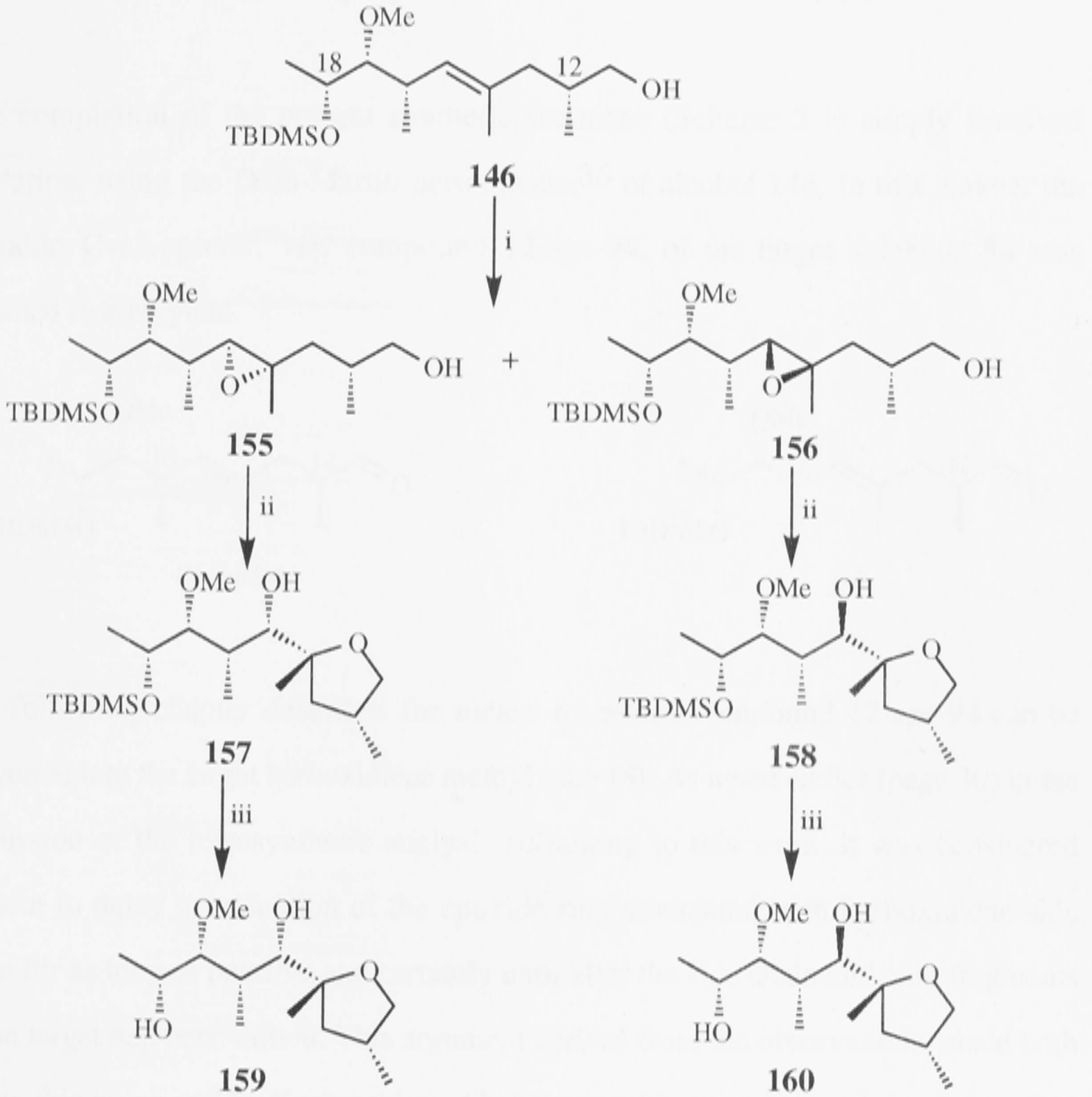


146

Figure 3.13: 75.5 MHz APT ^{13}C NMR Spectrum of Compound **146**.

(Spectrum recorded in $CDCl_3$ solution)

from the aforementioned Ireland-Claisen rearrangement posseses *R*- rather than the *S*-stereochemistry at C-12.

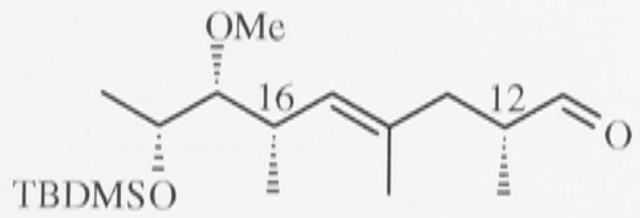


Scheme 3.3: Attempted Chemical Correlation Studies Aimed at Establishing the Stereochemistry at C-12 in Compound **146**.

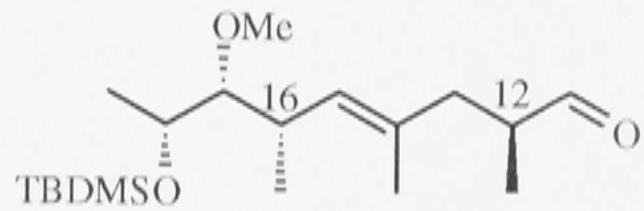
Reagents and conditions: (i) Dimethyldioxirane/acetone, -78 °C to rt; (ii) H^+ (trace); (iii) TBAF/THF, 0 °C to rt.

3.3 Completion of the Synthesis of the C-12 Epimer of the Target Aldehyde 94 Embodying C-11 to C-19 of Herboxidiene

The completion of the present synthetic sequence (Scheme 3.1) simply involved oxidation, using the Dess-Martin periodinane,[36] of alcohol **146**. In this manner the unstable C-12-epimer, *viz.* compound 12-*epi*-**94**, of the target aldehyde **94** was obtained in 80% yield.



12-*epi*-**94**



94

The following chapter describes the means by which compound 12-*epi*-**94** can be converted into the target herboxidiene methyl ester (**5**). As noted earlier (page 30) in the discussion of the retrosynthetic analysis pertaining to this work, it was considered prudent to delay introduction of the epoxide ring associated with herboxidiene side chain for as long as possible and certainly until after the side chain and core fragments of the target had been united. This argument derives from the observations, made both within this group and by Kocienski *et al*,[8] that once this epoxide ring is in place rather unstable molecules result that make handling and characterisation of such species very difficult.

CHAPTER FOUR

End Game: Union of Core and Side Chain Molecules with Subsequent Regio- and Diastereo-controlled Epoxidation Leading to Herboxidiene Methyl Ester (5)

4.1 Horner-Wittig Coupling of Phosphine Oxide 95 with C-12 epimer of the Aldehyde 94: Formation of Triene 161

With the ready acquisition, in enantiopure form, of both the phosphine oxide **95** and the aldehyde 12-*epi*-**94** the stage was now set for the crucial Horner-Wittig reaction, and, thence, the final stages of the total synthesis of herboxidiene. In the event (Scheme 4.1) coupling of the aldehyde and phosphine oxide could be effected using sodium hydride as base. This reaction was accompanied by C-12 epimerisation* of the former substrate as well as saponification of the initial coupling product (presumably due to the presence of residual base). As a consequence of the latter process the crude reaction mixture obtained on acidic work up was subjected to re-esterification with CH_2N_2. After this sequence of manipulations a 3:2 mixture of triene **161** (39%) $\{[\alpha]_D = +0.4$ (c = 2.3)$\}$ and its C-12-epimer **162** (26%) $\{[\alpha]_D = +18.4$ (c = 1.5)$\}$ was obtained.[9] These products could be separated from one another using semi-preparative HPLC techniques and the spectroscopic data obtained on the chromatographically less-mobile compound were in full accord with the assigned structure. However, as might be appreciated, it was very difficult to differentiate between these Horner-Wittig coupling products, *viz.* (compounds **161** and **162**) by comparison of the respective ^1H NMR spectra. It was fortunate, therefore, that in arbitrarily selecting the major fraction for elaboration, that this was correlated, chemically, with herboxidiene methyl ester (*vide infra*). The ^1H and ^{13}C NMR spectra of compound **161** are shown in Figures 4.1 and 4.2, respectively. The assignment of (*E*)-geometry to the newly installed $\Delta^{10,11}$-double-bond within product **161** follows from the model studies carried out by Bui *et al* [20] and from the conversion of this compound into herboxidiene methyl ester (**5**). Desilylation of compound **161** was accomplished using tetra-*n*-butylammonium flouride (TBAF) in THF and in this manner compound **163** (68%) was obtained.

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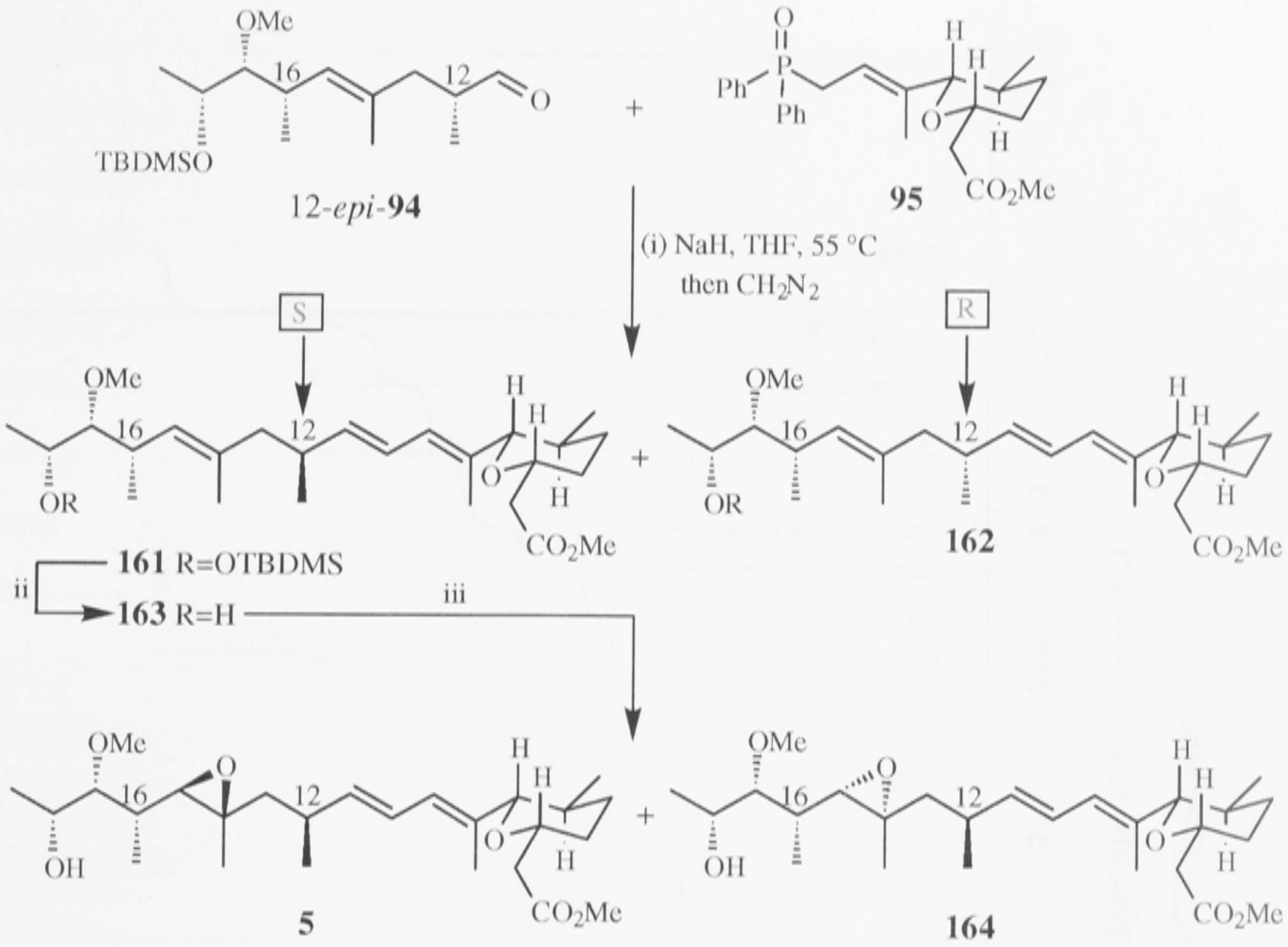
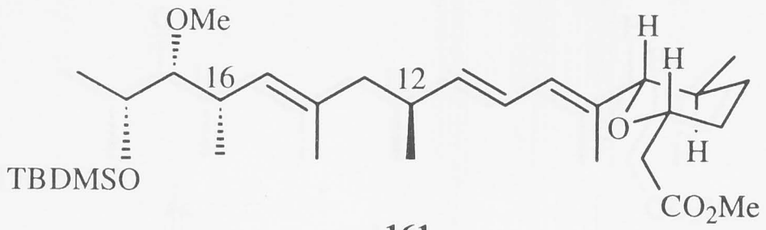
* This type of epimerisation was also observed by Smith and co-workers in their total synthesis of milbemycin β_3 and its C-12-epimer. The same group has reported that such epimerisation was not observed when a completely soluble base such as KHMDS was used.[50]



Scheme 4.1: Union of Core and Side Chain with Subsequent Regio- and Diastereo-controlled Epoxidation of the Resulting Triene **163**: Formation of Herboxidiene Methyl Ester (**5**).

Reagents and Conditions : (i) NaH/THF, 55 °C then CH_2N_2; (ii) TBAF/THF, 0 °C to rt.; (iii) *t*-BuOOH, $VO(acac)_2/CH_2Cl_2$, -8 °C, 72 h.



161

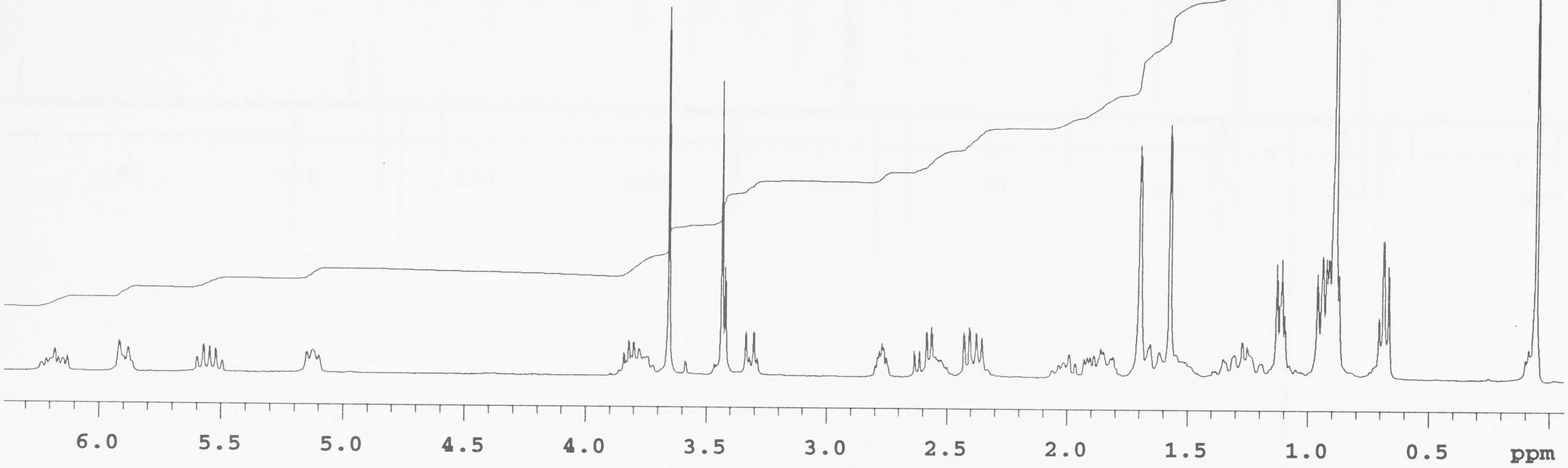
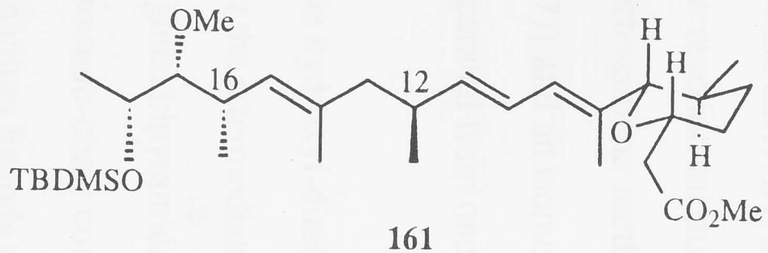


Figure 4.1: 300 MHz ^1H NMR Spectrum of Compound **161**.

(Spectrum recorded in $CDCl_3$ solution)



161

Figure 4.2: 75.5 MHz APT ^{13}C NMR Spectrum of Compound **161**.

(Spectrum recorded in $CDCl_3$ solution)

4.2 Regio- and Diastereo-controlled Epoxidation of Triene 163: Formation of Herboxidiene Methyl Ester (5)

Given the precedence afforded by Kocienski and Evans's work on directed epoxidation of *bis*-homoallylic alcohols,[9,17] a solution of alcohol **163** in CH_2Cl_2 was treated, at -8 °C, with 1 mole % of the catalyst vanadyl *bis*(acetylacetonate) [VO(acac)$_2$] then *tert*-butylhydroperoxide with the latter being added *via* a syringe pump over 48 h. After the addition was complete, the reaction mixture was allowed to stand at -8 °C for a further 24 h. These rather specific reaction conditions were considered necessary because of the observations made by Kocienski *et al* during the course of a related epoxidation reaction (see Chapter 1, page 23). Thus, it was expected that using more vigorous conditions could lead to nucleophilic attack of the C-18 hydroxy-group (within product **5**) at the newly formed epoxide ring and thereby producing tetrahydrofurans such as **2** (see Figure 1.1, page 6). The use of rather low catalyst loadings in the present reaction derives from the need to suppress *trans*-acylation reactions that would result in formation of the C-18 acetate derivatives of either the starting alkene and/or product epoxide. Upon work-up of the reaction mixture obtained on operating under these conditions a *ca.* 4:1 mixture of herboxidiene methyl ester (**5**) (73%) {$[\alpha]_D$ = +1.3 (c = 0.2)}, lit.[9] {$[\alpha]_D$ = +0.9 (c = 0.7)} and an isomer tentatively identified as **164** was produced. These epoxides could be separated from one another by semi-preparative HPLC.

The hydroxyl-directed epoxidation of *bis*-homoallylic alcohol **163** is believed to proceed *via* the intermediate shown in Figure 4.3 in which (i) the coordination geometry at V^{5+} is trigonal bipyramidal; (ii) the C-15 to C-18 position of the herboxidiene-type chain adopts a *pseudo*-chair conformation; (iii) steric interactions between the substituents and the vanadium ligands are minimised; and (iv) cleavage of the peroxide bond occurs from the backside along the axis of the O-O bond.[54,55] The intervention of such factors account

for the observed diastereofacially-selective epoxidation reaction with the resulting preferential formation of product **5** over isomer **164**.

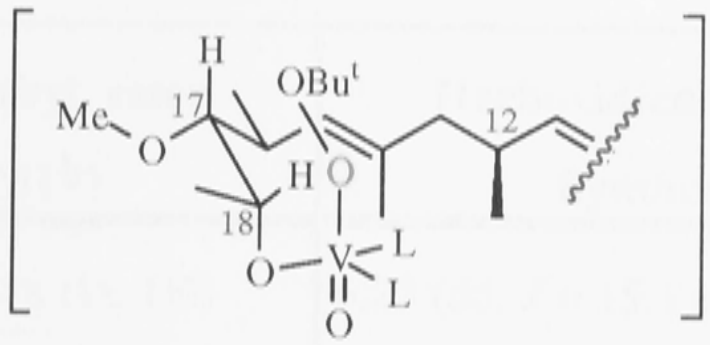


Figure 4.3: Likely Vanadate Intermediate Associated with the Hydroxyl-directed Epoxidation of Triene **163**.

The spectral data obtained on compound **5** matched, in all respects, those reported by Kocienski and co-workers[9] (Tables 4.1 and 4.2). The ^{1}H NMR spectrum of synthetically derived herboxidiene methyl ester (**5**) is shown in Figure 4.4 and is in full accord with the assigned structure. Analogous data could not be obtained on isomer **164** because of the small amount of material available so the assignment of the illustrated structure to this substance must remain tentative at this stage.

The acquisition of herboxidiene methyl ester (**5**) by the means described here constitutes a formal total synthesis of herboxidiene, since Kocienski and co-workers have simply saponified the C-1-ester functionality using K_2CO_3 in methanol in order to obtain the herboxidiene. During the course of the Horner-Wittig coupling reaction associated with the present work ready hydrolysis of the C-1-ester group was observed thus, suggesting the desired saponification should be readily achieved. The only reason for this step not having been carried out thus far is that insufficient quantities of the methyl ester **5** are available at the present time.

Table 4.1: Comparison of the 300 MHz ^{1}H NMR Spectral Data Obtained on that Sample of Herboxidiene Methyl Ester (**5**) Derived from Present Work with those Reported by Kocienski *et al.*[a]

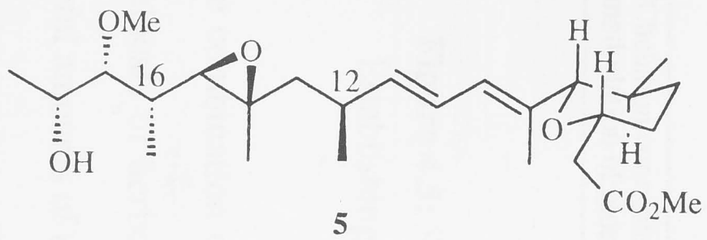
Herboxidiene Methyl ester Kocienski (δH[b])	**Herboxidiene Methyl ester Synthetic (δH)**
6.24 (dd, *J* = 15.0 and 10.8 Hz, 1H)	6.23 (dd, *J* = 15.3 and 10.6 Hz, 1H)
5.90 (d, *J* = 11.0 Hz, 1H)	5.90 (d, *J* = 10.9 Hz, 1H)
5.45 (dd, *J* = 14.9 and 8.8 Hz, 1H)	5.43 (dd, *J* = 14.9 and 8.8 Hz, 1H)
3.90-3.83 (m, 1H)	3.86-3.77 (m, 1H)
3.82-3.73 (m, 1H)	3.76-3.75 (m, 1H)
3.67 (s, 3H)	3.66 (s, 3H)
3.55 (s, 3H)	3.54 (s, 3H)
3.33 (d, *J* = 9.8 Hz, 1H)	3.32 (d, *J* = 9.8 Hz, 1H)
2.98 (t, *J* = 5.3 Hz, 1H)	2.97 (t, *J* = 5.4 Hz, 1H)
2.60 (dd, *J* = 15.2 and 6.2 Hz, 1H)	2.63-2.54 (complex m, 1H)
2.56 (d, J 9.7 Hz, 1H)	2.63-2.54 (complex m, 1H)
2.45-2.37 (m, 1H)	2.43-2.36 (complex m, 1H)
2.41 (dd *J* = 15.2 and 6.7 Hz, 1H)	2.43-2.36 (complex m, 1H)
1.90 (dd, *J* = 13.6 and 4.7 Hz, 1H)	1.92 (dd, *J* = 13.7 and 4.7 Hz, 1H)
1.88-1.81 (m, 1H)	1.86-1.81 (m, 1H)
1.71 (s, 3H)	1.70 (s, 3H)
1.70-1.50 (m, 3H)	1.67-1.56 (complex m, 3H)
1.40-1.20 (m, 3H)	1.54-1.30 (complex m, 3H)
1.29 (s, 3H)	1.28 (s, 3H)
1.19 (d, *J* = 6.4 Hz, 3H)	1.18 (d, *J* = 6.4 Hz, 3H)
1.05 (d, *J* = 6.7 Hz 3H)	1.04 (d, *J* = 6.7 Hz, 3H)
0.88 (d, *J* = 6.9 Hz 3H)	0.87 (d, *J* = 6.7 Hz, 3H)
0.67 (d, *J* = 6.6 Hz, 3H)	0.66 (d, *J* = 6.6 Hz, 3H)

[a] All data obtained using $CDCl_3$ as solvent; [b] Data obtained from reference 9.

Table 4.2: Comparison of the 75 MHz ^{13}C NMR Spectral Data Obtained on that Sample of Herboxidiene Methyl Ester (**5**) Derived from Present Work with those Reported by Kocienski *et al.*[a]

Herboxidiene Methyl Ester Kocienski (δC[b])	**Herboxidiene Methyl Ester Synthetic (δC)**
172.0 (0)	171.8 (0)
139.4 (1)	139.2 (1)
135.4 (0)	135.2 (0)
128.3 (1)	128.1 (1)
125.4 (1)	125.2 (1)
90.8 (1)	90.6 (1)
87.8 (1)	87.6 (1)
74.0 (1)	73.8 (1)
68.4 (1)	68.2 (1)
66.2 (1)	66.0 (1)
61.5 (0)	61.4 (3)
61.5 (3)	61.3 (0)
51.7 (3)	51.6 (3)
47.1 (2)	46.9 (2)
41.5 (2)	41.3 (2)
35.5 (1)	35.3 (1)
35.3 (1)	35.2 (1)
32.4 (2)	32.2 (2)
32.3 (1)	32.0 (1)
31.8 (2)	31.6 (2)
22.2 (3)	22.1 (3)
19.2 (3)	18.9 (3)
17.8 (3)	17.6 (3)
16.7 (3)	16.5 (3)
12.1 (3)	11.9 (3)
12.0 (3)	11.9 (3)

[a] All data obtained using $CDCl_3$ as solvent; [b] Data obtained from reference 9.



5

Figure 4.4: 300 MHz ^1H NMR Spectrum of Herboxidiene Methyl Ester (**5**).

(Spectrum recorded in $CDCl_3$ solution)

4.3 Summary

The formal total synthesis of herboxidiene described in the preceding sections of this thesis exploits the Katsuki-Sharpless asymmetric epoxidation, a chiral pool starting material and substrate-directed transformations for establishing the correct stereochemistry associated with eight of the nine centres of chirality contained in the target molecule. A summary of the relevant chemistry is provided in Figure 4.5.

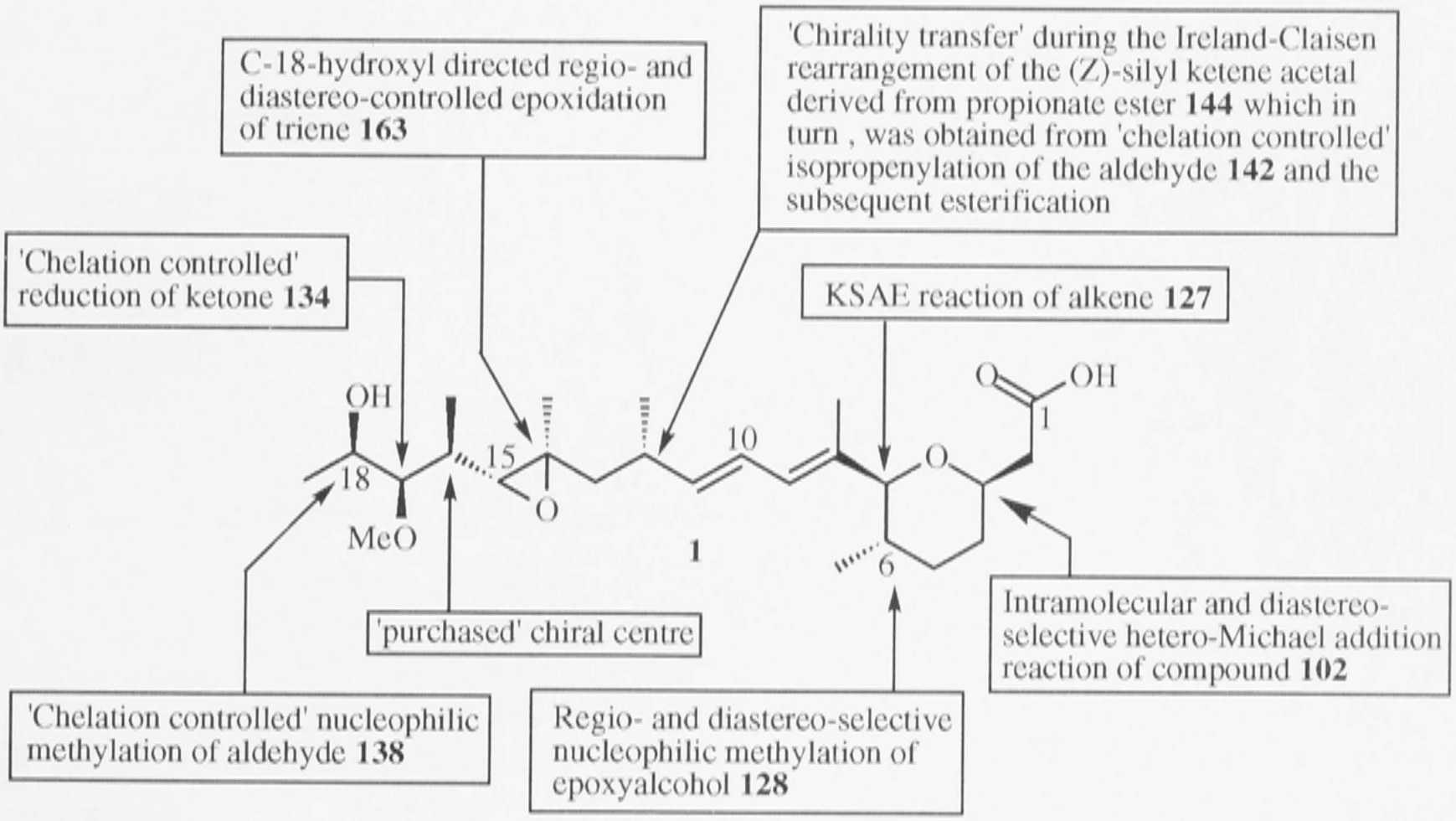


Figure 4.5: Substrate-directed Transformations used in the Present Work for Establishing the Correct Stereochemistry Associated with Herboxidiene (**1**).

The combination of such techniques has resulted in a reasonably concise formal total synthesis of herboxidiene. The present work provides good prospects for acquiring useful amounts of this natural product and a range of analogues that could be exploited in developing a detailed understanding of the SAR associated with this class of compound. Work directed toward these ends is now underway within these laboratories.

CHAPTER FIVE

Experimental Section

5.1 General Protocols

Proton (^{1}H) and carbon (^{13}C) NMR spectra were recorded on a Varian Gemini 300 spectrometer, operating at 300 MHz for proton and 75.4 MHz for carbon. All such spectra were recorded in deuterochloroform (chloroform-d) solution at 22 °C. Chemical shifts are recorded as δ values in parts per million (ppm). For ^{1}H NMR spectra recorded in deuterochloroform, the peak due to residual $CHCl_3$ (δ 7.26) was used as the internal reference. Data are recorded as follows: chemical shift (δ), multiplicity (s : singlet, d : doublet, t : triplet, q : quartet, m : multiplet, dd : doublet of doublets etc., br : broad), coupling constant(s) (*J* Hz), relative integral (for proton spectra) and assignment (where possible). The digital resolution within spectra varies slightly depending on the selection of spectral width and number of data points allocated to the time domain. However, in all cases this is, at worst, of the order of 0.4 Hz/point for one dimensional spectra. The protonicities of the carbon atoms observed in ^{13}C NMR spectra were determined by attached proton test (apt) experiments, *i.e.* by the phase of the resonance relative to the solvent signal, *viz.* C and CH_2 were of the same phase as the $CDCl_3$ triplet, whilst CH and CH_3 resonances were of the opposite phase. The central peak (δ 77.0) of the $CDCl_3$ triplet was used as the reference for $\{^{1}H\}^{13}C$ NMR spectra. APT ^{13}C NMR spectral data are recorded as follows: chemical shift (δ) and protonicity (C = quaternary, CH = methine, CH_2 = methylene, CH_3 = methyl, C/CH_2 = quaternary or methylene, CH/CH_3 = methine or methyl).

Infrared spectra were recorded with either a Perkin-Elmer 683G Infrared Spectrophotometer or a Perkin-Elmer 1800 Series Fourier Transform Infrared Spectrophotometer. Samples were analysed as thin liquid films on potassium bromide (KBr) plates.

Low and high resolution electron-impact mass spectra were recorded at 70 eV on a VG Fisons AUTOSPEC three sector (E / B / E) double-focussing Mass Spectrometer, using positive-ion electron impact techniques (unless otherwise

specified). Chemical ionisation (CI) mass spectra were recorded on the VG Fisons AUTOSPEC spectrometer, with NH_3 as the reactant gas. Mass spectral data are listed as mass-to-charge ratio (*m/z*), assignment (where possible) and relative intensity (% of base peak).

Optical rotations were measured using a Perkin-Elmer 241 Polarimeter at the sodium D line (589 nm) with spectroscopic grade chloroform as solvent (unless otherwise specified) at the temperature (T) and concentration (*c*) (g/100 mL) indicated in a cell with a path length (l) of 1 dm. Specific rotations $\{[\alpha]_D^T\}$ were calculated using the equation: $[\alpha]_D^T = (100.\alpha) / (l.c)$ and estimated to be within $\pm 0.05 \times 10^{-1}$ deg cm^2 g^{-1}.

Melting points were recorded with a Kofler hot stage apparatus and are uncorrected.

Ozonolyses were performed using a Wallace and Tiernan Ozonator with the oxygen flow rate and power adjusted to approximately 25 L/h and 200 V, respectively.

Analytical thin layer chromatography (TLC) was conducted on aluminium-backed 0.2 mm thick silica gel 60 F_{254} plates (Merck) and the chromatograms were visualised under a 254 nm UV lamp and/or by treatment with a reagent solution [either anisaldehyde/sulfuric acid/ethanol (2 : 5 : 93), phosphomolybdic acid/ethanol (8g : 200 ml) or phosphomolybdic acid/ceric (IV) sulfate/sulfuric acid/water (37.5 g / 7.5 g / 37.5 ml / 720 ml)] followed by heating with a hair dryer or on a hot plate. Flash chromatography was conducted according to the method of Still and co-workers[58] using 230-400 mesh silica and the analytical reagent (AR) grade solvents indicated.

High performance liquid chromatography (HPLC) was conducted on a Waters μ-Porasil™ semi-preparative silica column (7.8 x 300 nm) connected to an ISCO Model 2350 pump and eluting with the indicated HPLC-grade solvents. The peaks were detected using a Waters Lamda-Max Model 481 UV Detector connected to a Spectra-Physics SP4270 Reporting Integrator.

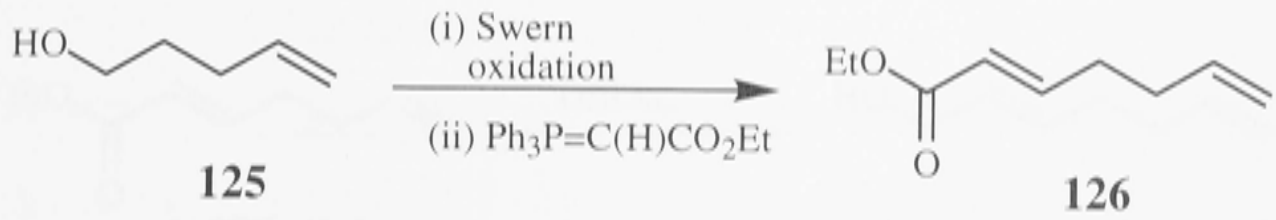
Many reagents were available from the Aldrich Chemical Company and were used as supplied. Drying agents and other inorganic salts were purchased from AJAX or BDH Chemicals. Reaction solvents and reagents were purified according to established

procedures.[59] The concentrations of alkyl lithium solutions obtained from Aldrich were determined by titration with *sec*-butanol (1.0 M solution in toluene) using 1,10-phenanthroline as indicator.[60] Tetrahydrofuran (THF) and diethyl ether (ether) were dried with sodium and then distilled under nitrogen from sodium benzophenone ketyl. Benzene, toluene, dichloromethane, hexane and *N*,*N*-dimethylformamide (DMF) were distilled from calcium hydride. Pyridine was distilled from and stored over potassium hydroxide pellets. Diisopropylamine was refluxed over calcium hydride for 4 h then distilled under vacuum and stored under nitrogen. Dimethyl sulfoxide (DMSO) was dried with 4 Å molecular sieves, then distilled and stored over 4 Å molecular sieves. Triethylamine was refluxed over calcium hydride for 2 h then distilled from calcium hydride and stored over potassium hydroxide pellets.

Reactions employing air- and/or moisture-sensitive reagents were carried out under an atmosphere of dry, oxygen-free nitrogen in oven- or flame-dried apparatus. Organic solutions obtained from work-up and/or extraction of reaction mixtures were dried with magnesium sulphate ($MgSO_4$) unless otherwise specified. Solutions were concentrated under reduced pressure on a rotary evaporator with the water bath temperature generally not exceeding 30 °C. When reactions were conducted at, or below 0 °C, the internal temperature was monitored using an alcohol thermometer.

5.2 Experimental Procedures Associated with Work Described in Chapter Two

Ethyl (*E*)-2,6-Heptadienoate (126)



125 **126**

DMSO (23.7 ml, 334 mmol) was added to a magnetically stirred solution of oxalyl chloride (13.4 ml, 153 mmol) in dichloromethane (480 ml) maintained under a nitrogen atmosphere at -78 °C. After 0.1 h 4-penten-1-ol (**125**) (12.0 g, 139 mmol, ex ALDRICH) was added, dropwise, followed, after a further 0.25 h, by triethylamine (134 ml, 961 mmol). The resulting mixture was stirred for 0.5 h at -78 °C then warmed to room temperature and treated with (carbethoxymethylene)triphenylphosphorane [56] (72.8 g, 209 mmol) in dry dichloromethane (110 ml). After 2 h at room temperature, the reaction mixture was quenched with water (200 ml) and the separated aqueous layer was extracted with dichloromethane (3 x 100 ml). The combined organic layers were washed with brine (1 x 75 ml) then dried, filtered and concentrated under reduced pressure to give a light-yellow oil. An ethyl acetate/hexane (1:9 v/v) solution of this material was filtered through a short pad of t.l.c. grade silica gel to afford, after concentration of the filtrate, the title ester **126**[26,28] (21.0 g, 98%) as a light-yellow oil. This material was of sufficient purity for use in the next step of the reaction sequence.

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.93 (dt, $J_{3,2}$ = 15.6 and $J_{3,4}$ = 5.7 Hz, 1H), 5.84-5.73 (complex m, 2H), 5.06-4.96 (complex m, 2H), 4.15 (q, J = 7.1 Hz, 2H), 2.32-2.17 (complex m, 4H), 1.26 (t, J = 7.1 Hz, 3H).

^{13}C NMR (75.5 MHz, $CDCl_3$) δ 166.5 (C), 148.2 (CH), 137.0 (CH), 121.6 (CH), 115.4 (CH_2), 60.1 (CH_2), 32.0 (CH_2), 31.4 (CH_2), 14.2 (CH_3).

IR (KBr plate, cm^{-1}) 3078, 2980, 2933, 1721, 1655, 1446, 1367, 1315, 1266, 1206, 1176, 1044, 989, 914, 852.

Mass Spectrum (70 eV) *m/z* (%) 154 ($M^{+\cdot}$, 6), 125 [$(M\text{-}C_2H_5\cdot)^+$, 6], 109 [$(M\text{-}C_2H_5O\cdot)^+$, 30), 81 [$(M\text{-}C_2H_5OCO\cdot)^+$, 100], 55 (34).

(*E*)-2,6-Heptadien-1-ol (127)

126 **127**

Diisobutylaluminium hydride (325 ml of a 1.0 M solution in hexane, 325 mmol, ex ALDRICH) was added, dropwise, *via* syringe to a magnetically stirred solution of ethyl (*E*)-2,6-heptadienoate (**126**) (20.0 g, 130 mmol) in dichloromethane (650 ml) maintained under a nitrogen atmosphere at -78 °C. The resulting mixture was stirred for 2 h at -78 °C and then warmed to 18 °C and quenched with tartaric acid (200 ml of a 1 M aqueous solution). Stirring was continued until two distinct layers were observed (0.25 h). The separated aqueous layer was extracted with dichloromethane (3 x 200 ml) and the combined organic phases were washed with brine (1 x 200 ml) then dried, filtered and concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 1:4 v/v ethyl acetate/hexane elution). Concentration of the appropriate fractions (R_f = 0.25) then afforded the title compound **127**[26,30] (12.4 g, 85%) as a light-yellow oil.

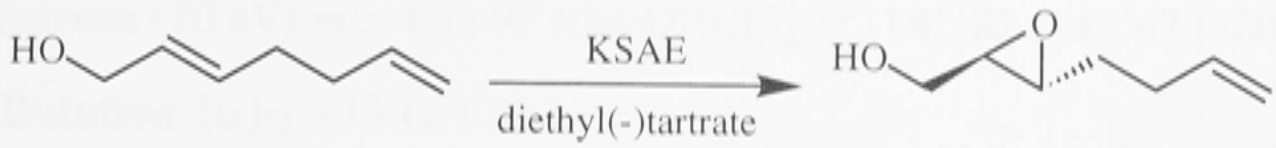
^{1}H NMR (300 MHz, $CDCl_3$) δ 5.85–5.65 (complex m, 3H), 5.04-4.94 (complex m, 2H), 4.07 (d, J = 4.4 Hz, 2H), 2.15-2.13 (complex m, 4H), 1.67 (s, 1H).

^{13}C NMR (75.5 MHz, $CDCl_3$) δ 138.0 (CH), 132.4 (CH), 129.3 (CH), 114.8 (CH_2), 63.7 (CH_2), 33.2 (CH_2), 31.5 (CH_2).

IR (KBr plate, cm^{-1}) 3326, 2923, 1641, 1437, 1087, 1000, 970, 911.

Mass Spectrum (70 eV) *m/z* (%) 111 [$(M\text{-}H\cdot)^+$, 1], 94 [$(M\text{-}HO\cdot)^+$, 13], 83 (13), 79 [$(M\text{-}C_2H_3O\cdot)^+$, 100], 70 (42), 66 (16), 57 (65).

(2R-*trans*)-2,3-Oxiranehept-6-en-1-ol [(+)-128]



127 **(+)-128**

A magnetically stirred suspension of finely powdered and activated 4 Å molecular sieves (1.0 g) in dry dichloromethane (137 ml) was cooled to -40 °C then treated, sequentially, with diethyl *D*-(-)-tartrate (0.92 ml, 5.38 mmol), Ti(O-*i*-Pr)$_4$ (1.32 ml, 4.50 mmol) and *tert*-butyl hydroperoxide (TBHP) (17.2 ml of a 5.2 M solution in isooctane, 89 mmol, prepared by iso-octane extraction of 70 % *tert*-butyl hydroperoxide ex ALDRICH[31]). The resulting mixture was stirred at -40 °C for 0.5 h then a solution of compound **127** (5.0 g, 44.64 mmol) in dichloromethane (20 ml) was added, *via* cannula, at such a rate as to maintain the reaction temperature below -20 °C. After an additional 3 h at -20 °C the reaction mixture was warmed to 0 °C then treated with water (26 ml). The reaction mixture was then warmed to 18 °C and after a further 1 h treated with NaOH (6.0 ml of a 30% aqueous solution saturated with sodium chloride) and stirred vigorously. After *ca.* 0.2 h of stirring, the mixture was filtered through a small pad of Celite™ then the separated aqueous layer was extracted with dichloromethane (3 x 150 ml). The combined organic layers were dried, filtered and concentrated under reduced pressure and the oily residue thus obtained was subjected to flash chromatography (silica, 3:7 v/v ethyl acetate/hexane elution). Concentration of the appropriate fractions (R_f = 0.3) then afforded the *title compound* (+)-***128*** (4.0 g, 70%) as a clear, colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.90-5.73 (complex m, 1H), 5.10-4.95 (complex m, 2H), 3.94-3.88 (complex m, 1H), 3.66-3.58 (complex m, 1H), 3.01-2.90 (complex m, 2H), 2.20 (m, 2H), 1.76 (t, J = 6.5 Hz, 1H), 1.71-1.64 (complex m, 2H).

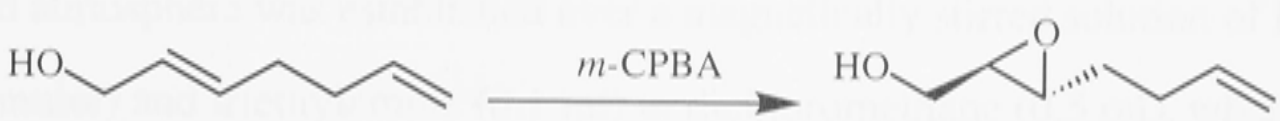
^{13}C NMR (75.5 MHz, $CDCl_3$) δ 137.4 (CH), 115.3 (CH_2), 61.7 (CH_2), 58.6 (CH), 55.4 (CH), 30.8 (CH_2), 30.1 (CH_2).

IR (KBr plate, cm^{-1}) 3401, 3078, 2979, 2928, 1641, 1449, 1088, 1030, 997, 914, 882, 720, 642.

Mass Spectrum (70 eV) *m/z* (%) 97 [$(M\text{-}OHCH_2\cdot)^+$, 18], 83 (14), 67 (100), 55 (75).

Specific Rotation $[\alpha]_D$ +33 (c 1.2)

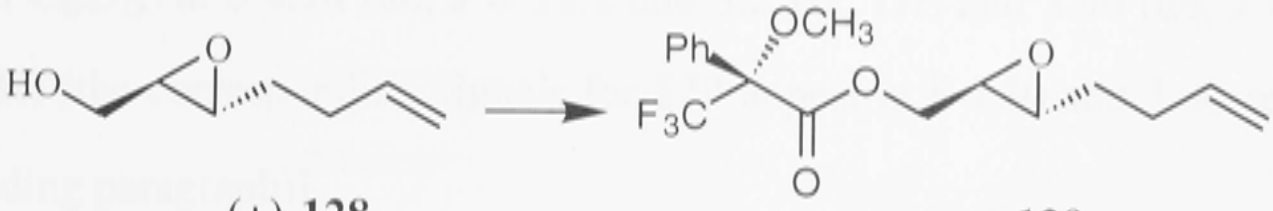
(±)-*trans*-2,3-Oxiranehept-6-en-1-ol [(±)-128]



127 **(±) 128**

A magnetically stirred solution of allylic alcohol **127** (50 mg, 0.45 mmol) in dichloromethane (2.5 ml) was treated, portionwise, with *m*-chloroperbenzoic acid (132 mg of technical grade material containing *ca.* 70% peracid, *ca.* 0.54 mmol). After 2 h the reaction mixture was quenched with $Na_2S_2O_5$ (5 ml of a 1.0 M aqueous solution). The separated organic phase was washed with $NaHCO_3$ (1 x 5 ml) and water (1 x 5 ml) then dried, filtered and concentrated under reduced pressure to give a light-yellow oil. Subjection of this material to flash chromatography (silica, 1:4 v/v ethyl acetate/hexane elution) followed by concentration of the appropriate fractions (R_f = 0.3) then afforded the *title compound* (±)-***128*** (25 mg, 44%) as a clear, colourless oil. This material was identical, as judged by ^1H NMR, ^{13}C NMR and infrared spectroscopic analysis, with the material obtained using the KSAE protocol described above.

Mosher Ester Analysis of Epoxides (+)-128 and (±)-128. Formation of Ester 129 and a Diastereoisomer there-of.



(+)-128 **129**

A nitrogen atmosphere was established over a magnetically stirred solution of DMAP (18 mg, 0.15 mmol) and triethylamine (0.1 ml) in dichloromethane (0.5 ml), which was then treated with epoxy-alcohol (+)-**128** (19.2 mg, 0.15 mmol) and (+)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride[31] (0.04 ml. 0.20 mmol). The resulting solution became warm and turned orange in colour. After 0.1 h the reaction mixture was treated with $NaHCO_3$ (5 ml of a saturated aqueous solution) and extracted with dichloromethane (2 x 10 ml). The combined organic extracts were washed with brine (1 x 5 ml) then dried, filtered and concentrated under reduced pressure to afford a pale-yellow oil which was subjected to flash chromatography (silica, 1:4 v/v ethyl acetate/hexane elution). Concentration of the appropriate fractions (R_f = 0.4) afforded *Mosher ester* ***129*** (21.7 mg, 42%) as a clear colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82 (d, *J* = 7.6 Hz, 2H), 7.35-7.05 (complex m, 3H), 5.69 (m, 1H), 5.00 (m, 2H), 4.30 (dd, *J* = 12.2 and 3.2 Hz, 1H), 3.80 (dd, *J* = 12.2 and 5.8 Hz, 1H), 3.54 (s, 3H), 2.63 (m, 1H), 2.53 (m, 1H), 1.97 (m, 2H), 1.32 (m, 2H).

^{13}C NMR (75.5 MHz, C_6D_6) δ 166.9 (C), 138.0 (CH), 133.1 (C), 130.2 (CH), 129.1 (CH), 127.9 (CH), 127.9 (CH), 127.8 (CH), 126.5 (C), 122.6 (C), 115.7 (CH_2), 66.1 (CH_2), 55.9 (CH_3), 55.8 (CH), 55.8 (CH), 31.2 (CH_2), 31.0 (CH_2).

The racemic epoxide (±)-**128** (25 mg, 0.2 mmol) was converted into the corresponding mixture of diastereoisomeric Mosher esters by reaction with (+)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride under the conditions described immediately

above. ^{1}H NMR and ^{13}C NMR spectroscopic analysis of this material revealed it to be a 1:1 mixture of compound **129** and the diastereoisomeric ester derived from *ent*- **128**. The most diagnostic ^{1}H NMR signals due to the (*R*)-MTPA ester derivative of *ent*-**128** appear (in C_6D_6) at δ 4.14 (dd, *J* = 12.2 and 3.2 Hz, 1H) and 3.90 (dd, *J* = 12.2 and 5.8 Hz, 1H) [the corresponding signals for **129** appear at δ 4.30 and 3.80 respectively (see preceding paragraph)].

(2*S*,3*S*)-3-Methyl-6-heptene-1,2-diol (130)

(+)-128 **130**

Me3Al (131 ml of a 2.0 M solution in hexane, 262 mmol, ex ALDRICH) was added, dropwise, to a magnetically stirred solution of epoxide (+)-**128** (11.15 g, 87 mmol) in dichloromethane (90 ml) maintained at 0 °C under a nitrogen atmosphere. After addition was complete, the reaction mixture was stirred at 18 °C for 10 h and then chilled (0 °C) and quenched (CAUTION) with HCl (75 ml of a 1 M aqueous solution). The aqueous layer was extracted with dichloromethane (3 x 150 ml) and the combined organic layers washed with water (1 x 100 ml) then dried, filtered and concentrated under reduced pressure. The oily residue obtained in this manner was subjected to flash chromatography (silica, 1:1 v/v ethyl acetate/hexane elution). Concentration of the appropriate fractions (R_f = 0.4) then afforded the *title compound* ***130*** (10.41 g, 83%) as a clear, colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.78 (m, 1H), 5.03-4.88 (complex m, 2H), 3.70-3.60 (complex m, 1H), 3.53-3.40 (complex m, 2H), 3.20 (br s, 2H), 2.20-2.08 (complex m, 1H), 2.05-1.90 (complex m, 1H), 1.70-1.54 (complex m, 2H), 1.29-1.18 (complex m, 1H), 0.88 (d, *J* = 7.0 Hz, 3H).

^{13}C NMR (75.5 MHz, $CDCl_3$) δ 138.8 (CH), 114.5 (CH_2), 76.1 (CH), 64.6 (CH_2), 35.5 (CH), 31.6 (CH_2), 31.1 (CH_2), 15.1 (CH_3).

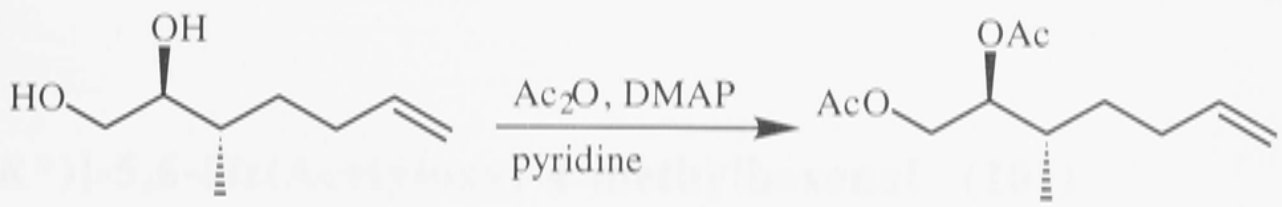
IR (KBr plate, cm^{-1}) 3368, 3077, 2962, 2928, 1640, 1458, 1380, 1073, 995, 909, 880, 637.

Mass Spectrum (70 eV) *m/z* (%) 145.1 ($M+H^+$, 3), 144 ($M^{+\cdot}$, 3), 143 [$(M-H\cdot)^+$, 2], 126 (33), 111 (36), 108 (12), 101 (15), 95 (100), 87 (10), 83.1, (24), 79 (25), 71 (53), 61 (48), 55 (76).

HRMS calcd for $C_8H_{16}O_2$ $(M-H\cdot)^+$, 143.1072. Found: $(M-H\cdot)^+$, 143.1070.

Specific Rotation $[\alpha]_D$ -5.7 (c 1.2)

(2*S*,3*S*)-3-Methyl-6-heptene-1,2-diol Diacetate (131)



130 **131**

A magnetically stirred solution of diol **130** (5.54 g, 38.5 mmol) in pyridine (21 ml) was treated with acetic anhydride (12.7 ml, 134 mmol) and 4-(*N*,*N*-dimethylamino)pyridine (10 mg, 0.08 mmol). The resulting mixture was stirred at 18 °C for 3 h then poured onto ice (*ca.* 50 g) and extracted with ether (1 x 100 ml). The separated organic phase was washed with HCl (2 x 20 ml of a 1M aqueous solution), $NaHCO_3$ (2 x 20 ml of a saturated aqueous solution) and brine (1 x 20 ml) then dried, filtered and concentrated under reduced pressure. The oily residue thus obtained was subjected to flash chromatography (silica, 3:7 v/v ethyl acetate/hexane elution) and concentration of the appropriate fractions (R_f = 0.65) then afforded the *title compound* ***131*** (8.40 g, 96%) as a clear, colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.76 (m, 1H), 5.03-4.90 (complex m, 3H), 4.27 (dd, *J* = 12.0 and 3.0 Hz, 1H), 4.05 (dd, *J* = 12.0 and 4.2 Hz, 1H), 2.15-1.90 (complex

m, 2H), 2.06 (s, 3H), 2.03 (s, 3H), 1.85-1.73 (complex m, 1H), 1.50 (m, 1H), 1.23 (m, 1H), 0.92 (d, J = 6.9 Hz, 3H).

^{13}C NMR (75.5 MHz, $CDCl_3$) δ 170.8 (C), 170.6 (C), 138.2 (CH), 114.8 (CH_2), 74.9 (CH), 63.6 (CH_2), 33.6 (CH), 31.3 (CH_2), 31.0 (CH_2), 21.0 (CH_3), 20.9 (CH_3), 15.0 (CH_3).

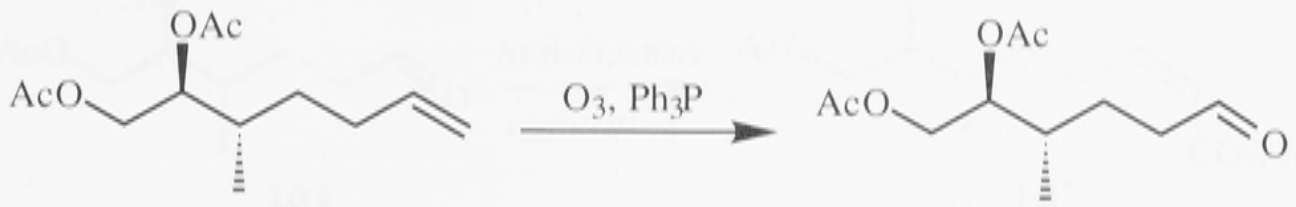
IR (KBr plate, cm^{-1}) 2973, 2937, 1744, 1641, 1458, 1371, 1227, 1048, 1020, 913, 605.

Mass Spectrum (70 eV) *m/z* (%) 229 ($M+H^+$, 2), 213 [$(M-H_3C\cdot)^+$, 24], 169 (38), 145 (18), 126 (42), 115 (76), 114 (78), 108 (90), 95 (100), 93 (96), 86 (38), 79 (70), 67 (64), 55 (76).

HRMS calcd for $C_{12}H_{21}O_4$ ($M+H^+$), 229.1439. Found: ($M+H^+$), 229.1439.

Specific Rotation $[\alpha]_D$ +5.24 (c 1.3)

[*S*-(*R, *R**)]-5,6-*bis*(Acetyloxy)-4-methylhexenal (101)**



131 **101**

A magnetically stirred solution of diacetate **131** (10.50 g, 45.65 mmol) in dichloromethane (575 ml) was cooled to -78 °C then treated with a stream of ozone gas until a blue colour persisted. The reaction mixture was then warmed to -30 °C and triphenyl phosphine (12.0 g, 45.65 mmol) was carefully added in portions. After the addition was complete, the reaction mixture was allowed to warm to room temperature then concentrated under reduced pressure. The residue there-by obtained was subjected to flash chromatography (silica, 3:7 v/v ethyl acetate/hexane elution). Concentration of the appropriate fractions (R_f = 0.3) gave the title compound **101**[20] (8.37 g, 79%) as a pale-yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.77 (s, 1H), 4.94 (m, 1H), 4.31 (dd, *J* = 12.1 and 2.9 Hz, 1H), 4.05 (dd, *J* = 12.1 and 6.8 Hz, 1H), 2.60-2.30 (complex m, 2H), 2.07 (s, 3H), 2.04 (s, 3H), 1.90-1.72 (complex m, 2H), 1.54-1.44 (complex m, 1H), 0.93 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR (75.5 MHz, $CDCl_3$) δ 201.8 (CH), 170.8 (C), 170.6 (C), 74.5 (CH), 63.4 (CH_2), 41.2 (CH_2), 33.5 (CH), 24.1 (CH_2), 21.0 (CH_3), 20.8 (CH_3), 15.1 (CH_3).

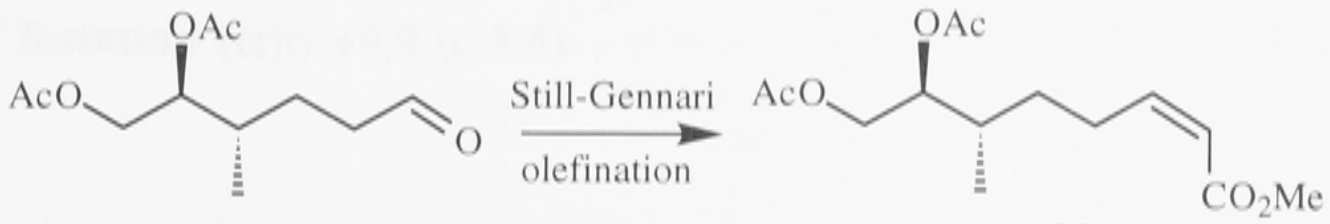
IR (KBr plate, cm^{-1}) 2967, 2727, 1744, 1371, 1227, 1048, 959, 605.

Mass Spectrum (70 eV) *m/z* (%) 231 ($M+H^+$, 15), 213 (6), 187 (23), 171 (27), 157 (8), 145 (38), 126 (33), 115 (60), 103 (53), 97 (100), 84 (48), 72 (38).

HRMS calcd for $C_{11}H_{18}O_5$ $(M+H)^+$, 231.1232. Found: $(M+H)^+$, 231.1232.

Specific Rotation $[\alpha]_D$ +7.3 (c 2.0 in MeOH)

Methyl {*S*-[*R,*R**-(*Z*)]}-7,8-*bis*(Acetyloxy)-6-methyl-2-octenoate (102)**



101 **102**

KHMDS (73.0 ml of a 0.5 M solution in toluene, 36.52 mmol) was added, dropwise, to a magnetically stirred solution of bis(2,2,2-trifluoroethyl) (methoxycarbonylmethyl)phosphonate (7.73 ml, 36.5 mmol) and 18-crown-6/CH_3CN complex[57] (48.3 g, 183 mmol) in dry THF (140 ml) maintained at -78 °C under an atmosphere of nitrogen. The reaction mixture was stirred at -78 °C for 0.5 h then treated with aldehyde **101** (8.40 g, 36.52 mmol). After 1 h at this temperature, the reaction mixture was quenched with NH_4Cl (60 ml of a saturated aqueous solution) then allowed to warm to room temperature. The resulting mixture was extracted with ether (3 x 50 ml) and the combined organic phases were washed with water (1 x 100 ml) then

dried, filtered and concentrated under reduced pressure. The oily residue thus obtained was subjected to flash chromatography (silica, 3:7 v/v ethyl acetate/hexane elution) and concentration of the appropriate fractions (R_f = 0.4) gave the title ester **102**[20] (8.35 g, 80%) as a pale-yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.18 (m, 1H), 5.78 (br. d, *J* = 11.5 Hz, 1H), 4.95 (td, *J* = 6.8 and 2.9 Hz, 1H), 4.29 (dd, *J* = 12.0 and 2.9 Hz, 1H), 4.06 (dd, *J* = 12.0 and 7.1 Hz, 1H), 3.70 (s, 3H), 2.68 (m, 2H), 2.07 (s, 3H), 2.04 (s, 3H), 1.82 (m, 1H), 1.65-1.50 (complex m, 1H), 1.35-1.20 (complex m, 1H), 0.96 (d, *J* = 7.0 Hz, 3H).

^{13}C NMR (75.5 MHz, $CDCl_3$) δ 170.8 (C), 170.6 (C), 166.7 (C), 149.8 (CH), 119.7 (CH), 74.9 (CH_3), 63.5 (CH_2), 51.0 (CH), 33.9 (CH), 31.3 (CH_2), 26.3 (CH_2), 21.0 (CH_3), 20.8 (CH_3), 15.0 (CH_3).

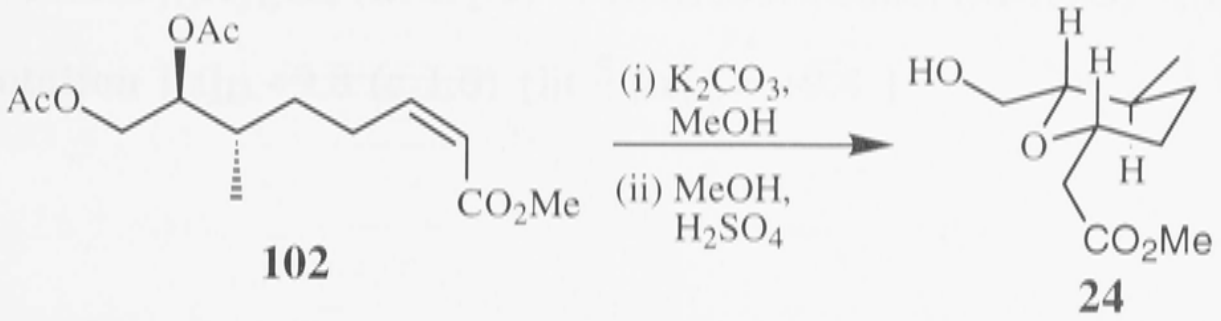
IR (KBr plate, cm^{-1}) 2953, 1743, 1645, 1439, 1371, 1226, 1176, 1048, 821.

Mass Spectrum (70 eV) *m/z* (%) 287 ($M+H^+$, 5), 255 (10), 226 (10), 213 (27), 194 (35), 184 (29), 166 (52), 153 (70), 139 (100), 107 (74), 81 (90), 72 (34).

HRMS calcd for $C_{14}H_{22}O_6$ $(M+H)^+$, 287.1494. Found: $(M+H)^+$, 287.1495.

Specific Rotation $[\alpha]_D$ +9.9 (c 5.4)

Methyl [2*R*-(2α,5ß,6α)]-Tetrahydro-6-(hydroxymethyl)-5-methyl-2*H*-pyran-2-acetate (24)



102 **24**

A mixture of ester **102** (8.35 g, 29.20 mmol), K_2CO_3 (20.20 g, 146 mmol) and methanol (42 ml) was stirred at 18 °C for 24 h then filtered through a sintered-glass funnel. Water (100 ml) was added to the filtrate which was acidified to pH 2-3 with

HCl (concentrated aqueous solution). The resulting mixture was extracted with diethyl ether (3 x 50 ml) and the combined extracts dried, filtered and then concentrated under reduced pressure. The light-yellow oil obtained in this manner was suspended in methanol (50 ml) containing H_2SO_4 (six drops of 98% acid) and the resulting mixture stirred at 18 °C for 16 h and then poured onto crushed ice (50 g) and extracted with diethyl ether (3 x 50 ml). The combined organic extracts were washed with $NaHCO_3$ (1 x 50 ml of a saturated aqueous solution) then dried, filtered and concentrated under reduced pressure. The ensuing oily residue was subjected to flash chromatography (silica, 3:7 v/v ethyl acetate/hexane elution) and concentration of the appropriate fractions ($R_f = 0.25$) then afforded the title compound **24**[20] (4.18 g, 71%) as a clear, colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 3.80–3.63 (complex m, 2H), 3.65 (s, 3H), 3.47 (ddd, J = 11.4, 7.1 and 4.3 Hz, 1H), 3.10 (ddd, J = 9.8, 7.1 and 2.7 Hz, 1H), 2.53 (dd, J = 15.2 and 7.7 Hz, 1H), 2.40 (dd, J = 15.2 and 5.4 Hz, 1H), 2.21 (dd, J = 8.2 and 4.4 Hz, 1H), 1.80-1.72 (complex m, 1H), 1.70-1.60 (complex m, 1H), 1.48-1.12 (complex m, 3H), 0.80 (d, J = 6.5 Hz, 3H).

^{13}C NMR (75.5 MHz, $CDCl_3$) δ 171.6 (C), 83.5 (CH), 74.0 (CH), 63.7 (CH_2), 51.6 (CH_3), 41.1 (CH_2), 32.1 (CH_2), 31.5 (CH_2), 31.1 (CH), 17.1 (CH_3).

IR (KBr plate, cm^{-1}) 3458 br, 2928, 2873, 1738, 1437, 1199, 1087, 1019.

Mass Spectrum (70 eV) *m/z* (%) 203 ($M+H^+$, 26), 184 (23), 171 [($M-H_3CO\cdot)^+$, 100)], 139 (73), 129 (57), 111 (49), 97 (54), 81 (36), 71 (48), 55 (46).

HRMS calcd for $C_{10}H_{18}O_4$ $(M-H_2O)^{+\cdot}$, 184.1099. Found: $(M-H_2O)^{+\cdot}$, 184.1097.

Specific Rotation $[\alpha]_D$ +9.8 (c 1.0) {lit.[5] $[\alpha]_D$ = +9.4 }

Methyl [2*R*-(2α,5ß,6α)]-6-Formyltetrahydro-5-methyl-2*H*-pyran-2-acetate (103)

24 **103**

A solution of alcohol **24** (1.0 g, 4.95 mmol) and triethylamine (4.5 ml, 32.1 mmol) in dichloromethane (14.2 ml) was added, dropwise, to a magnetically stirred solution of sulfur trioxide/pyridine complex (2.52 g, 15.84 mmol, ex ALDRICH) in dimethyl sulfoxide/dichloromethane (15.6 ml of a 3:2 v/v mixture) maintained at 0 °C (ice-bath) under a nitrogen atmosphere. The resulting mixture was warmed to 18 °C and stirred for a further hour before being quenched with water (130 ml) and extracted with hexane (3 x 75 ml). The combined organic phases were washed with brine (1 x 50 ml) then dried, filtered and concentrated under reduced pressure. The oily residue thus obtained was subjected to flash chromatography (silica, 3:7 v/v ethyl acetate/hexane elution) and concentration of the appropriate fractions (R_f = 0.4) afforded the title compound **103**[20] (594 mg, 60%) as a clear, colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.51 (d, *J* = 2.3 Hz, 1H), 3.80 (m, 1H), 3.67 (s, 3H), 3.41 (dd, *J* = 10.6 and 2.3 Hz, 1H), 2.61 (dd, *J* = 15.4 and 7.6 Hz, 1H), 2.44 (dd, *J* = 15.4 and 5.4 Hz, 1H), 1.88 (m, 1H), 1.70 (m, 1H), 1.64-1.50 (complex m, 1H), 1.45-1.20 (complex m, 2H), 0.91 (d, *J* = 6.6 Hz, 3H).

^{13}C NMR (75.5 MHz, $CDCl_3$) δ 200.6 (CH), 171.4 (C), 86.7 (CH), 73.5 (CH), 51.7 (CH_3), 41.0 (CH_2), 32.1 (CH_2), 30.8 (CH_2), 30.5 (CH), 16.3 (CH_3).

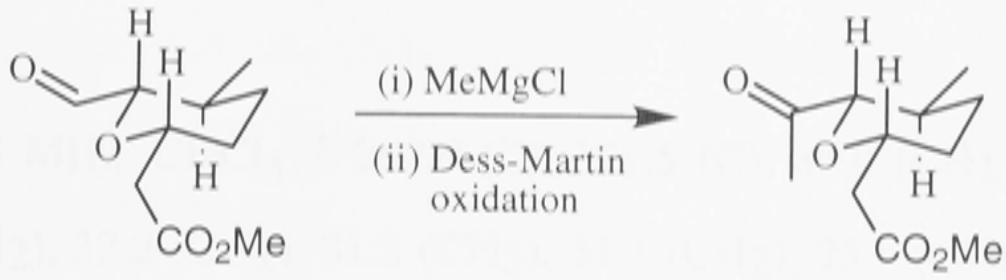
IR (KBr plate, cm^{-1}) 2932, 1740, 1437, 1200, 1090, 1021, 857.

Mass Spectrum (70 eV) *m/z* (%) 201 ($M+H^+$, 14), 183 (17), 171 [$(M\text{-}CHO\cdot)^+$, 100], 139 (88), 127 (52), 121 (26), 111 (57), 97 (88), 81 (57), 69 (59), 55 (66).

HRMS calcd for $C_{10}H_{16}O_4$ $(M\text{-}CHO\cdot)^+$, 171.1021. Found: $(M\text{-}CHO\cdot)^+$, 171.1020.

Specific Rotation $[\alpha]_D$ -65 (c 0.45) {lit.[5] $[\alpha]_D$ = -62 (c 0.5 in $CHCl_3$)}

Methyl [2*R*-(2α,5ß,6α)]-6-Acetyltetrahydro-5-methyl-2*H*-pyran-2-acetate (13)



103 **13**

Methylmagnesium chloride (0.83 ml of a 3 M solution in THF, 2.5 mmol, ex ALDRICH) was added, dropwise, to a magnetically stirred solution of aldehyde **103** (500 mg, 2.5 mmol) in THF (12.5 ml) maintained at -78 °C under a nitrogen atmosphere. After the addition was complete the reaction mixture was allowed to warm to 0 °C stirred at this temperature for a further 1 h then poured onto a mixture of ice (*ca.* 20 g) and NH_4Cl (20 ml of a saturated aqueous solution). The resulting mixture was extracted with ether (3 x 20 ml) and the combined organic phases were washed with water (1 x 30 ml) then dried, filtered and concentrated under reduced pressure. The oily residue thus obtained was subjected to flash chromatography (silica, 3:7 v/v ethyl acetate/hexane elution) and concentration of the appropriate fractions (R_f = 0.3) afforded a diastereoisomeric mixture of secondary alcohols (190 mg, 35 %) as a clear, colourless oil. This material was dissolved in dichloromethane (8.0 ml) and the resulting solution treated with the Dess-Martin periodinane[36] (560 mg, 1.32 mmol). The mixture thus obtained was stirred at 18 °C for 1 h then diluted, successively, with diethyl ether (10 ml), $NaHCO_3$ (5 ml of a saturated aqueous solution) and $Na_2S_2O_3$ (5 ml of a 1 M aqueous solution). Stirring was continued until two layers become apparent. The separated aqueous phase was extracted with diethyl ether (3 x 10 ml) and the combined organic phases were washed with brine (1x 10 ml) then dried, filtered and concentrated under reduced pressure. The resulting light-yellow oil was subjected to flash chromatography (silica, 3:7 v/v ethyl acetate/hexane elution) and concentration of the appropriate fractions (R_f = 0.3) then afforded the title compound **13**[20] (90 mg, 17%) as a clear, colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 3.78 (m, 1H), 3.67 (s, 3H), 3.41 (d, *J* = 10.2 Hz, 1H), 2.57 (dd, *J* = 15.1 and 7.6 Hz, 1H), 2.44 (dd, *J* = 15.1 and 5.4 Hz, 1H), 2.14 (S, 3H), 1.87 (m, 1H), 1.72-1.67 (complex m, 1H), 1.60-1.18 (complex m, 3H), 0.82 (d, *J* = 6.6 Hz, 3H).

^{13}C NMR (75.5 MHz, $CDCl_3$) δ 207.9 (C), 171.5 (C), 89.0 (CH), 73.7 (CH), 51.7 (CH_3), 41.1 (CH_2), 32.2 (CH_2), 31.8 (CH_3), 31.1 (CH_2), 25.8 (CH), 16.9 (CH_3).

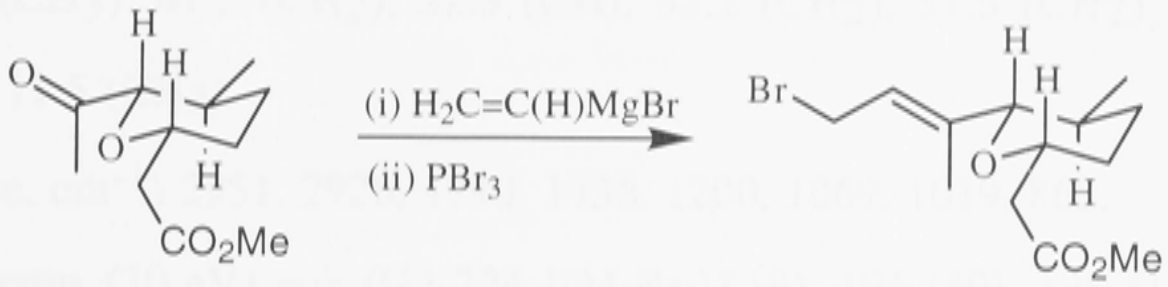
IR (KBr plate, cm^{-1}) 2931, 1741, 1719, 1437, 1354, 1199, 1083, 1022, 894.

Mass Spectrum (70 eV) *m/z* (%) 215 ($M+H^+$, 5), 183 (10), 171 [($M-CH_3CO\cdot)^+$, 100], 139 (95), 121 (27), 111 (61), 97 (92), 83 (44), 69 (49), 55 (58).

HRMS calcd for $C_{11}H_{18}O_4$ $(M+H)^+$, 215.1283. Found: $(M+H)^+$, 215.1282.

Specific Rotation $[\alpha]_D$ -91 (c 1.2) {lit.[5] $[\alpha]_D$ = -95 (c 1.5 in $CHCl_3$)

Methyl {2*R*-[2α,5ß,6α(*E*)}-6-(3-Bromo-1-methyl-1-propenyl)tetrahydro-5-methyl-2*H*-pyran-2-acetate (106)



13 **106**

Vinylmagnesium bromide (1.60 ml of a 1 M solution in THF, 1.58 mmol, ex ALDRICH) was added, dropwise, to a magnetically stirred solution of ketone **13** (339 mg, 1.58 mmol) in THF (65 ml) maintained at -78 °C under a nitrogen atmosphere. The resulting mixture was stirred at -78 °C for a further 1 h then warmed to 0 °C, poured into NH_4Cl (25 ml of a saturated aqueous solution) and extracted with diethyl ether (3 x 50 ml). The combined organic extracts were dried, filtered and concentrated under reduced pressure to give a light-yellow oil (203 mg) which was subjected to flash chromatography (silica, 1:4 v/v ethyl acetate/hexane elution). Concentration of the appropriate fractions (R_f = 0.3) then afforded the expected vinyl alcohol **105.** This material was immediately subjected to

the brominative rearrangement reaction. Thus, PBr_3 (50 µl, 0.50 mmol) was injected, *via* syringe, into a magnetically stirred solution of vinyl alcohol (100 mg, 0.41 mmol) in diethyl ether (10 ml) maintained at 0 °C under a nitrogen atmosphere. After the addition was complete, the reaction mixture was stirred at 0 °C for a further 1 h and then poured onto crushed ice (*ca.* 10 g). The resulting mixture was extracted with diethyl ether (1 x 30 ml) and the separated organic phase dried, filtered and then concentrated under reduced pressure. Subjection of this material to flash chromatography (silica, 1:4 v/v ethyl acetate/hexane elution) afforded, after concentration of the appropriate fractions (R_f = 0.3), the title bromide **106**[20] (117 mg, 93%) as a clear, colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.69 (t, *J* = 9.0 Hz, 1H), 4.00 (m, 2H), 3.80-3.70 (complex m, 1H), 3.66 (s, 3H), 3.35 (d, *J* = 9.8 Hz, 1H), 2.58 (dd, *J* = 15.2 and 6.5 Hz, 1H), 2.40 (dd, *J* = 15.2 and 6.5 Hz, 1H), 1.90-1.80 (complex m, 1H), 1.69 (s, 3H), 1.70-1.65 (complex m, 1H), 1.62-1.47 (complex m, 1H), 1.40-1.15 (complex m, 2H), 0.71 (d, *J* = 6.7 Hz, 3H).

^{13}C NMR (75.5 MHz, $CDCl_3$) δ 171.7 (C), 141.5 (C), 123.9 (CH), 89.5 (CH), 73.8 (CH), 51.6 (CH_3), 41.2 (CH_2), 32.3 (CH), 32.2 (CH_2), 31.5 (CH_2), 28.2 (CH_2), 17.4 (CH_3), 11.5 (CH_3).

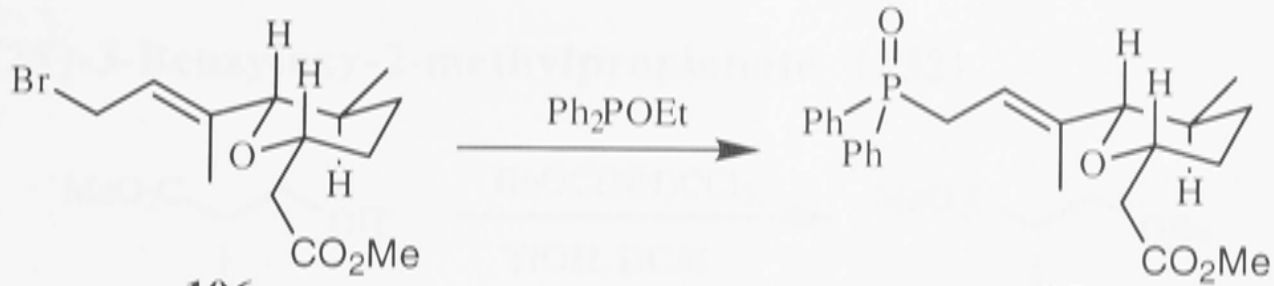
IR (KBr plate, cm^{-1}) 2951, 2926, 1740, 1436, 1200, 1069, 1019, 865.

Mass Spectrum (70 eV) *m/z* (%) 224 [$(M\text{-}Br\cdot)^+$, 8), 194 (49), 178 (13), 134 (46), 121 (100).

HRMS calcd for $C_{13}H_{21}BrO_3$ $(M\text{-}Br\cdot)^+$, 225.1491. Found: $(M\text{-}Br\cdot)^+$, 225.1495.

Specific Rotation $[\alpha]_D$ -29 (c 2.1) {lit[20] $[\alpha]_D$ = -5.2 (c 1.5 in $CHCl_3$)}

Methyl {2*R*-[2α,5ß,6α(*E*)}-6-[3-Diphenylphosphinoyl)-1-methyl-1-propenyl]tetrahydro-5-methyl-2*H*-pyran-2-acetate (95)



106 **95**

A magnetically stirred solution of bromide **106** (100 mg, 0.33 mmol) and diphenylethoxyphosphine (143 µl, 0.66 mmol ex ALDRICH)) in THF (10 ml) was heated at reflux until the starting materials had been consumed (*ca.* 2 h). The cooled reaction mixture was then concentrated under reduced pressure and the resulting solid recrystallised (diethyl ether) to give the phosphine oxide **95**[20] (119 mg, 85%) as a fine white powder, mp 125-126 °C {lit.[20] m.p. 125-126 °C}.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.74 (m, 4H), 7.50 (m, 6H), 5.50 (m, 1H), 3.72-3.60 (complex m, 1H), 3.63 (s, 3H), 3.26 (d, *J* = 9.7 Hz, 1H), 3.23-3.10 (complex m, 2H), 2.54 (dd, *J* = 15.1 and 6.5 Hz, 1H), 2.37 (dd, *J* = 15.1 and 6.4 Hz, 1H), 1.78-1.60 (complex m, 2H), 1.47 (s, 3H), 1.45-1.10 (complex m, 3H), 0.42 (d, *J* = 6.6 Hz, 3H).

^{13}C NMR (75.5 MHz, $CDCl_3$) δ 171.7 (C), 140.0 (d, C), 133.2 (d, C), 131.9 (CH), 131.0 (d, CH), 128.5 (d, CH), 116.9 (d, CH), 90.0 (CH), 73.8 (CH), 51.5 (CH_3), 41.3 (CH_2), 32.1 (CH_2), 32.0 (CH_3), 31.5 (CH_2), 30.7 (d, CH_2), 17.2 (CH), 12.2 (CH_3) [d = doublet (due to ^{13}C-^{31}P coupling)]. **^{31}P NMR** δ 31.0.

IR (KBr disc, cm^{-1}) 2924, 2847, 1736, 1437, 1180, 1120, 1069, 1018, 745, 719, 697, 555, 512.

Mass Spectrum (70 eV) *m/z* (%) 426 ($M^{+\cdot}$, 51), 395 (10), 324 (16), 285 (16), 216 (14), 203 (28), 202 [$(Ph_2POH)^{+\cdot}$, 100], 201 [$(Ph_2PO)^{+\cdot}$, 94], 77 (24).

HRMS calcd for $C_{25}H_{31}O_4P$ ($M^{+\cdot}$), 426.1960. Found: ($M^{+\cdot}$), 426.1962.

Specific Rotation $[\alpha]_D$ -0.4 (c 1.4)

5.3 Experimental Procedures Associated with Work Described in Chapter Three

Methyl (2*S*)-3-Benzyloxy-2-methylpropionate (132)

96 **132**

Tifluoromethanesulfonic acid (3.40 ml, 38.1 mmol) was added, *via* syringe, to a magnetically stirred solution of methyl (2*S*)-3-hydroxy-2-methylpropionate **96** (15.0 g, 127 mmol, ex SIGMA) and benzyl 2,2,2-trichloroacetimidate (28.3 ml, 152.4 mmol) in a mixture of cyclohexane (200 ml) and dichloromethane (100 ml) maintained under a nitrogen atmosphere at 0 °C (ice bath). The reaction mixture was allowed to warm to room temperature, stirred for 16 h then filtered through a sintered glass funnel. The filtrate was washed with $NaHCO_3$ (1 x 200 ml of a saturated aqueous solution) and water (1 x 200 ml) then dried, filtered and concentrated under reduced pressure. The oily residue thus obtained was subjected to flash chromatography (silica, 1:9 v/v ethyl acetate/hexane elution) and concentration of the appropriate fractions (R_f = 0.25) afforded the *title compound* ***132*** (25.6 g, 97%) as a clear, colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30-7.38 (complex m, 5H), 4.52 (s, 2H), 3.70 (s, 3H), 3.68 (dd, *J* = 8.7 and 7.3 Hz, 1H), 3.50 (dd, *J* = 9.1 and 5.9 Hz, 1H), 2.81-2.75 (complex m, 1H), 1.18 (d, *J* = 7.1 Hz, 3H).

^{13}C NMR (75.5 MHz, $CDCl_3$) δ 175.6 (C), 138.4 (C), 128.6 (CH), 127.9 (CH), 127.8 (CH), 73.3 (CH_2), 72.2 (CH_2), 52.0 (CH_3), 40.4 (CH), 14.2 (CH_3).

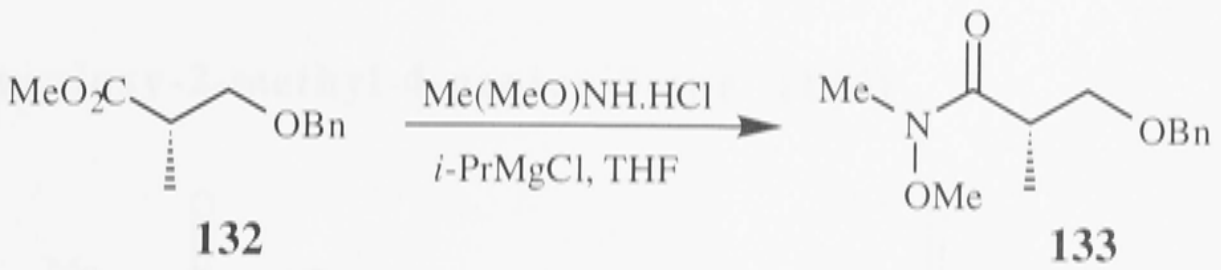
IR (KBr plate, cm^{-1}) 2862, 1740, 1455, 1201, 1098, 738, 699.

Mass Spectrum (70eV) m/z (%) 208 ($M^{+\cdot}$, 9), 177 [$(M\text{-}CH_3O\cdot)^+$, 4], 121 (16), 107 (53), 91 (100).

HRMS calcd for $C_{12}H_{16}O_3$ ($M^{+\cdot}$), 208.1099. Found: ($M^{+\cdot}$), 208.1096.

Specific Rotation $[\alpha]_D$ +12.5 (c 2.4)

(2*S*)-3-Benzyloxy-*N*-methoxy-*N*-methyl-2-methylpropanamide (133)



132 **133**

Isopropylmagnesium chloride(155.8 ml of a 2.0 M solution in THF, 311.5 mmol, ex ALDRICH) was added, steadily and over 0.5 h, to a magnetically stirred suspension of ester **132** (21.6 g, 103.8 mmol) and *N*, *O*-dimethylhyroxylamine hydrochloride (15.7 g, 161.0 mmol) in THF (230 ml) maintained under a nitrogen atmosphere at -15 °C. The resulting mixture was stirred for 0.5 h at -15 °C by which time TLC analysis revealed complete consumption of the starting material. At this point the reaction was quenched with NH_4Cl (150 ml of a saturated aqueous solution), diluted with water (150 ml) and extracted with diethyl ether (3 x 100 ml). The combined organic extracts were washed with brine (1 x 100 ml) then dried, filtered and concentrated under reduced pressure. The oily residue thus obtained was subjected to flash chromatography (silica, 3:7 v/v ethyl acetate/hexane elution) and concentration of the appropriate fractions ($R_f = 0.3$) afforded the *Weinreb amide* ***133*** (23.4 g, 95%) as a clear, colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34-7.27 (complex m, 5H), 4.52 (m, 2H), 3.72 (app. t., J = 8.6 Hz, 1H) 3.70 (s, 3H), 3.43 (dd, J = 8.8 and 5.9 Hz, 1H), 3.25 (m, 1H), 3.22 (s, 3H), 1.12 (d, J = 7.1 Hz, 3H).

^{13}C NMR (75.5 MHz, $CDCl_3$) δ 175.8 (C), 138.3 (C), 128.2 (CH), 127.5 (CH), 127.4 (CH), 73.1 (CH_2), 72.5 (CH_2), 61.5 (CH_3), 35.8 (CH), 32.2 (CH_3), 14.2 (CH_3).

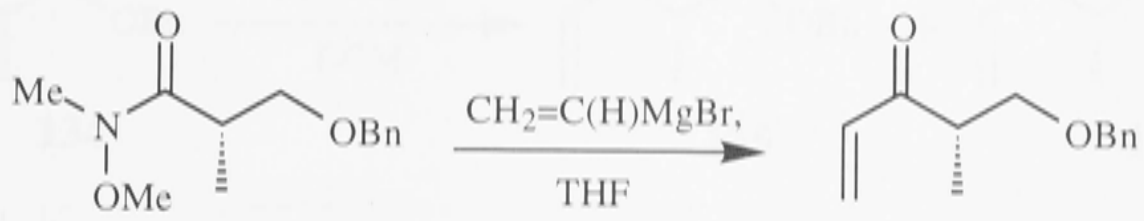
IR (KBr plate, cm^{-1}) 2862, 1660, 1454, 1102, 994, 739, 699.

Mass Spectrum (70eV) m/z (%) 238 ($M+H^+$, 11), 206 [$(M-CH_3O\cdot)^+$, 11], 177 (25), 131 (70), 91 (100), 77 (44), 65 (58).

HRMS calcd for $C_{13}H_{20}NO_3$ ($M+H^+$), 238.1443. Found: ($M+H^+$), 238.1442.

Specific Rotation $[\alpha]_D$ +4.62 (c 2.0)

(2*S*)-1-Benzyloxy-2-methyl-4-penten-3-one (134)



133 **134**

Vinylmagnesium bromide (126.4 ml of a 1.0 M solution in THF, 126.4 mmol, ex ALDRICH) was added, dropwise, to a magnetically stirred solution of Weinreb amide **133** (20.0 g, 84.3 mmol) in THF (833 ml) maintained under a nitrogen atmosphere at 0 °C (ice bath). The reaction mixture was stirred for a further 0.5 h at this temperature and then quenched with NH_4Cl (450 ml of a saturated aqueous solution). The aqueous layer was extracted with diethyl ether (3 x 250 ml) and the combined organic extracts were washed with brine (1 x 300 ml) then dried, filtered and concentrated under reduced pressure. The oily residue thus obtained was subjected to flash chromatography (silica, 1:4 v/v ethyl acetate/hexane elution) and concentration of the appropriate fractions (R_f = 0.5) afforded the *title ketone **134*** (15.8 g, 92%) as a pale-yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35-7.25 (complex m, 5H), 6.45 (dd, *J* = 17.5 and 10.4 Hz, 1H), 6.25 (dd, *J* = 17.5 and 1.5 Hz, 1H), 5.79 (dd, *J* = 10.4 and 1.5 Hz, 1H), 4.49 (m, 2H), 3.70 (dd, *J* = 9.2 and 8.4 Hz, 1H), 3.47 (dd, *J* = 9.2 and 5.9 Hz, 1H), 3.18 (m, 1H), 1.12 (d, *J* = 7.0 Hz, 3H).

^{13}C NMR (75.5 MHz, $CDCl_3$) δ 202.5 (C), 138.1 (CH_2), 135.5 (CH), 128.4 (C), 128.3 (CH), 127.5 (C), 73.2 (CH_2), 72.0 (CH_2), 43.6 (CH), 13.9 (CH_3).

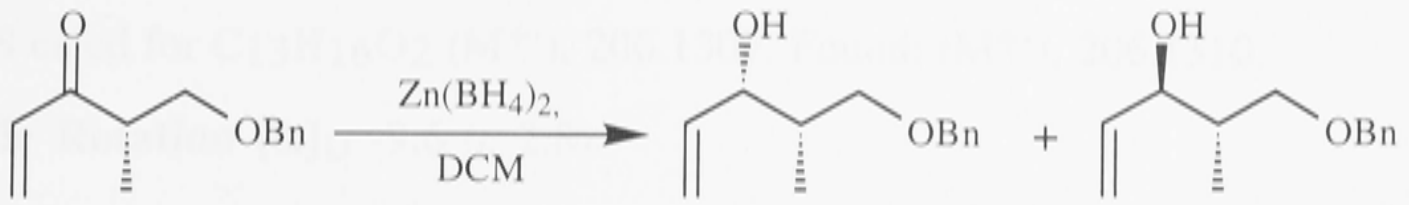
IR (KBr plate, cm^{-1}) 2859, 1697, 1454, 1198, 1101, 1028, 737, 698.

Mass Spectrum (70eV) m/z (%) 205 ($M+H^+$, 10), 107 (35), 98 (75), 91 (100), 77 (25), 65 (35).

HRMS calcd for $C_{13}H_{17}O_2$ ($M+H^+$), 205.1229, Found: ($M+H^+$), 205.1226.

Specific Rotation $[\alpha]_D$ +13.5 (c 2.8)

(3*S*, 4*S*)-4-Methyl-5-(phenylmethoxy)-1-penten-3-ol (135) and (3*R*, 4*S*)-4-Methyl-5-(phenylmethoxy)-1-penten-3-ol (136)



134 **135** **136**

Zinc borohydride (318.1 ml of a 0.43 M solution in diethyl ether, 136.8 mmol, which was prepared from zinc chloride and sodium borohydride[44]) was added, dropwise, to a magnetically stirred solution of vinyl ketone **134** (18.6 g, 91.2 mmol) in dichloromethane (890 ml) maintained under a nitrogen atmosphere at -78 °C. The resulting mixture was stirred for 2 h at -78 °C then warmed (0 °C) and stirred for a further 0.5 h. The reaction was quenched by transferring the reaction mixture *via* cannula to a rapidly stirred solution of HCl (600 ml of a 1 M aqueous solution) maintained at 0 °C. The aqueous layer was extracted with dichloromethane (3 x 250 ml) and the combined organic extracts were washed successively with $NaHCO_3$ (1 x 250 ml of a saturated aqueous solution) and brine (1 x 250 ml) then dried, filtered and concentrated under reduced pressure. The ensuing oily residue was then subjected to HPLC (μ-Porasil 40 x 100 mm cartridge column, 1:9 v/v ethyl acetate/hexane elution, flow rate 30 ml/min) and two fractions, A and B, were obtained.

Concentration of fraction A (R_t 12 min) afforded *compound **135*** (15.4 g, 82%) as a clear, colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39-7.28 (complex m, 5H), 5.88 (ddd, J = 17.2, 10.6 and 5.4 Hz, 1H), 5.33-5.16 (complex m, 2H), 4.51 (s, 2H), 4.28-4.25 (complex m, 1H), 3.56-3.49 (complex m, 2H), 3.0 (br. s, 1H), 2.12-2.05 (complex m, 1H), 0.91 (d, J = 7.0 Hz, 3H)

^{13}C NMR (75.5 MHz, $CDCl_3$) δ 138.5 (CH), 137.9 (CH_2), 128.3 (CH), 127.6 (CH), 127.55 (CH), 115.0 (C), 75.0 (CH), 73.6 (CH_2), 73.3 (CH_2), 38.2 (CH), 11.5 (CH_3).

IR (KBr plate, cm^{-1}) 3440, 2966, 2860, 1454, 1097, 737, 698.

Mass Spectrum (70eV) m/z (%) 206 ($M^{+\cdot}$, 19), 188 (26), 144 (56), 108 (46), 91 (100).

HRMS calcd for $C_{13}H_{16}O_2$ ($M^{+\cdot}$), 206.1307. Found: ($M^{+\cdot}$), 206.1310.

Specific Rotation $[\alpha]_D$ -9.6 (c 2.8).

Concentration of fraction B (R_t 16.5 min) afforded *compound* ***136*** (3.4 g, 18 %) as a clear, colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35-7.29 (complex m, 5H), 5.88 (ddd, *J* = 17.2, 10.6 and 5.4 Hz, 1H), 5.29-5.13 (complex m, 2H), 4.52 (s, 2H), 4.03 (t, *J* = 6.7 Hz, 1H), 3.62 (dd, *J* = 9.3 and 4.3 Hz, 1H), 3.47 (dd, *J* = 9.3 and 7.2 Hz, 1H), 3.37 (br. s, 1H), 1.91 (m, 1H), 0.91 (d, *J* = 7.1 Hz, 3H).

^{13}C NMR (75.5 MHz, $CDCl_3$) δ 139.7 (CH), 138.1 (CH_2), 128.7 (CH), 128.2 (CH), 128.0 (CH), 127.9 (CH), 116.1 (C), 76.9 (CH), 74.8 (CH_2), 73.7 (CH_2), 38.8 (CH), 14.0 (CH_3).

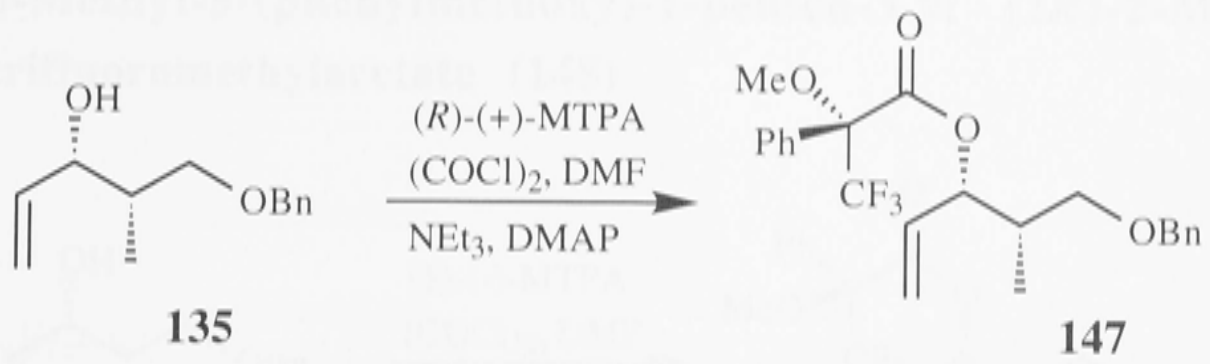
IR (KBr plate, cm^{-1}) 3430, 2962, 2857, 1454, 1097, 737, 698.

Mass Spectrum (70eV) m/z (%) 206 ($M^{+\cdot}$, 37), 188 (54), 144 (82), 108 (50), 91 (100).

HRMS calcd for $C_{13}H_{16}O_2$ ($M^{+\cdot}$), 206.1307. Found: ($M^{+\cdot}$), 206.1308.

Specific Rotation $[\alpha]_D$ +28.2 (c 2.5).

(3*R*, 4*S*)-4-Methyl-5-(phenylmethoxy)-1-penten-3-yl (2*R*)-2-Methoxy-2-phenyl-2-trifluoromethylacetate (147)



135 **147**

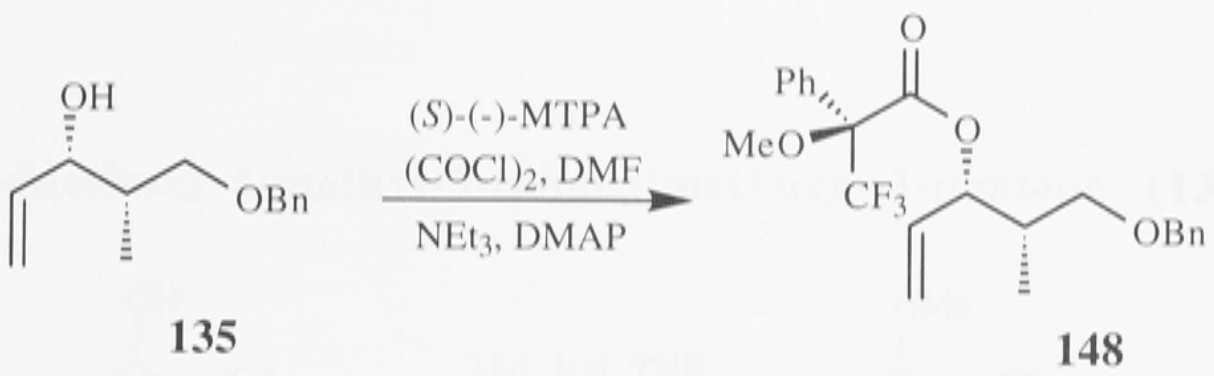
Oxalyl chloride (12.5 µl, 0.14 mmol) followed by *N*, *N*-dimethylformamide (1 drop) was added to a magnetically stirred solution of (*R*)-(+)-MTPA (74 mg, 0.32 mmol) in dichloromethane (2 ml) maintained at 0 °C (ice bath) under a nitrogen atmosphere. The reaction mixture was allowed to warm to room temperature, stirred for a further 0.75 h and then transferred, *via* cannula, to a chilled (0 °C) and magnetically stirred solution of the alcohol **135** (24 mg, 0.12 mmol), triethylamine (34 µl, 0.24 mmol) and DMAP (2 mg) in dichloromethane (3 ml). The cold bath was removed and the reaction mixture was stirred at room temperature for 16 h. The solution was then partitioned between dichloromethane (10 ml) and $NaHCO_3$ (10 ml of a saturated aqueous solution) and the phases separated. The aqueous layer was extracted with dichloromethane (3 x 10 ml) and the combined organic fractions were washed with brine (1 x 10 ml) then dried, filtered and concentrated under reduced pressure to give a pale-yellow oil. Subjection of the crude material to flash chromatography (silica, 1:4 v/v ethyl acetate/hexane elution) provided, after concentration of the appropriate fractions (R_f = 0.4), the *title compound* ***147*** (27 mg, 55%) as a clear, colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53-7.30 (complex m, 10H), 5.84 (ddd, *J* = 17.2, 10.4 and 7.0 Hz, 1H), 5.67 (dd, *J* = 7.1 and 4.4 Hz, 1H), 5.30 (dd, *J* = 18.4 and 10.4 Hz, 2H), 4.40 (d, *J* = 5.9 Hz, 2H), 3.53 (s, 3H), 3.26 (dd, *J* = 6.1 and 2.7 Hz, 2H), 2.10 (m, 1H), 0.90 (d, *J* = 6.9 Hz, 3H).

^{13}C NMR (75.5 MHz, $CDCl_3$) δ 165.8 (C), 138.3 (CH_2), 133.9 (CH), 132.6 (C), 129.6 (CH), 128.44 (CH), 128.37 (CH), 127.6 (CH), 127.51 (CH), 127.48 (CH),

121.6 (C), 119.6 (C), 115.2 (C), 77.9 (CH), 73.2 (CH_2), 71.5 (CH_2), 55.4 (CH_3), 37.9 (CH), 11.5 (CH_3).

(3*R*, 4*S*)-4-Methyl-5-(phenylmethoxy)-1-penten-3-yl (2*R*)-2-Methoxy-2-phenyl-2-trifluoromethylacetate (148)



135 **148**

Oxalyl chloride (25 µl, 0.29 mmol) followed by *N*, *N*-dimethylformamide (1 drop) was added to a magnetically stirred solution of (*S*)-(-)-MTPA (120 mg, 0.51 mmol) in dichloromethane (2 ml) maintained at 0 °C (ice bath) under a nitrogen atmosphere. The reaction mixture was allowed to warm to room temperature, and stirred for a further 0.75 h and then transferred, *via* cannula, to a chilled (0 °C) and magnetically stirred solution of the alcohol **135** (50 mg, 0.24 mmol), triethylamine (68 µl, 0.48 mmol) and DMAP (2 mg) in dichloromethane (3 ml). The cold bath was removed and the reaction mixture was stirred at room temperature for 16 h. The solution was then partitioned between dichloromethane (10 ml) and $NaHCO_3$ (10 ml of a saturated aqueous solution) and the phases separated. The aqueous layer was extracted with dichloromethane (3 x 10 ml) and the combined organic fractions were washed with brine (1 x 10 ml) then dried, filtered and concentrated under reduced pressure to give a pale-yellow oil. Subjection of the crude material to flash chromatography (silica, 1:4 v/v ethyl acetate/hexane elution) provided, after concentration of the appropriate fractions (R_f = 0.4), the *title compound* ***148*** (48 mg, 47 %) as a clear, colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52-7.30 (complex m, 10H), 5.76 (dd, *J* = 10.6 and 4.0 Hz, 1H), 5.68 (complex m, 2H), 5.24 (d, *J* = 16.5 Hz, 1H), 5.23 (d, *J* = 11.0 Hz, 1H), 4.50 (d, *J* = 1.8 Hz, 2H), 3.50 (s, 3H), 3.34 (d, *J* = 6.6 Hz, 2H), 2.12-2.08 (complex m, 1H), 0.96 (d, *J* = 7.0 Hz, 3H).

^{13}C NMR (75.5 MHz, $CDCl_3$) δ 165.8 (C), 138.2 (CH_2), 133.8 (CH), 132.2 (C), 129.6 (CH), 128.41 (CH), 128.35 (CH), 128.3 (CH), 127.63 (CH), 127.58 (CH), 127.56 (CH), 121.5 (C), 118.3 (C), 77.8 (CH), 73.2 (CH_2), 71.6 (CH_2), 55.4 (CH_3), 37.6 (CH), 11.6 (CH_3).

(3*S*, 4*S*)-3-Methoxy-4-methyl-5-(phenylmethoxy)-1-pentene (137)

135 **137**

A solution of alcohol **135** (4.50 g, 21.8 mmol) in THF (20 ml) was added, dropwise, to a magnetically stirred suspension of KH (6.3 g of 35% (w/w) dispersion in mineral oil, 54.6 mmol) in THF (150 ml) maintained under a nitrogen atmosphere. The resulting mixture was stirred at room temperature for 0.25 h then chilled (0 °C) and treated, *via* syringe, with a solution of methyl iodide (3.4 ml, 54.6 mmol) in THF (25 ml). The reaction mixture was then allowed to warm to room temperature and stirred for a further 0.25 h then cautiously poured onto ice (50 g). The resulting mixture was extracted with ether (3 x 200 ml) and the combined organic phases were dried, filtered and concentrated under reduced pressure. The ensuing oily residue was subjected to flash chromatography (silica, 1:9 v/v ethyl acetate/hexane elution) and concentration of the appropriate fractions (R_f = 0.6) afforded the *title bis-ether* ***137*** (4.1 g, 85%) as a clear, colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35-7.27 (complex m, 5H), 5.69 (ddd, *J* = 16.5, 10.9 and 7.7 Hz, 1H), 5.24-5.17 (complex m, 2H), 4.50 (s, 2H), 3.62 (t, *J* = 7.0 Hz, 1H), 3.51 (dd, *J* = 8.1 and 4.5 Hz, 1H), 3.31 (dd, *J* = 9.0 and 6.4 Hz, 1H), 3.27 (s, 3H), 1.94-1.85 (complex m, 1H), 0.96 (d, *J* = 7.1 Hz, 3H)

^{13}C NMR (75.5 MHz, $CDCl_3$) δ 138.7 (C), 137.1 (CH), 128.3 (CH), 127.6 (CH), 127.47 (CH), 127.45 (CH), 117.4 (CH_2), 83.5 (CH), 73.1 (CH_2), 72.4 (CH_2), 56.8 (CH_3), 38.5 (CH), 12.2 (CH_3).

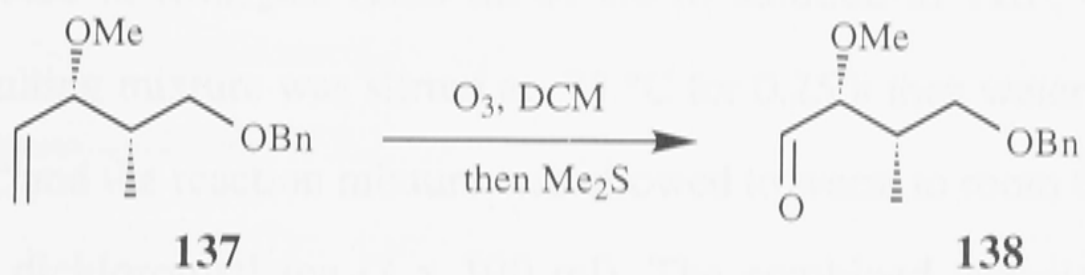
IR (KBr plate, cm^{-1}) 2902, 2856, 1454, 1095, 925, 736, 698.

Mass Spectrum (70eV) m/z (%) 220 ($M^{+\cdot}$, 20), 205 (15), 188 (11), 129 (16), 112 (16), 91 (83), 71 (100), 67 (24).

HRMS calcd for $C_{14}H_{20}O_2$ ($M^{+\cdot}$), 220.1463. Found: ($M^{+\cdot}$), 220.1464.

Specific Rotation $[\alpha]_D$ +12.2 (c 1.3).

(2*R*, 3*S*)-2-Methoxy-3-methyl-4-(phenylmethoxy)butanal (138)



137 **138**

A magnetically stirred solution of alkene **137** (2.0 g, 9.1 mmol) in dichloromethane (200 ml) was cooled to -78 °C then treated with a stream of ozone gas until a blue colour persisted. The reaction mixture was warmed to -30 °C and then dimethyl sulfide (1.3 ml, 18.2 mmol) was added in small portions. The reaction mixture was allowed to warm to room temperature and the solvent was removed under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 1:9 v/v ethyl acetate/hexane elution) and concentration of the appropriate fractions (R_f = 0.4) afforded the *title aldehyde* ***138*** (1.45 g, 72%) as a clear, colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.68 (d, *J* = 1.5 Hz, 1H), 7.35-7.29 (complex m, 5H), 4.50 (q, *J* = 12.0 and 5.6 Hz, 2H), 3.74-3.39 (complex m, 3H), 3.43 (s, 3H), 2.33-2.30 (complex m, 1H), 0.91 (d, *J* = 7.1 Hz, 3H)

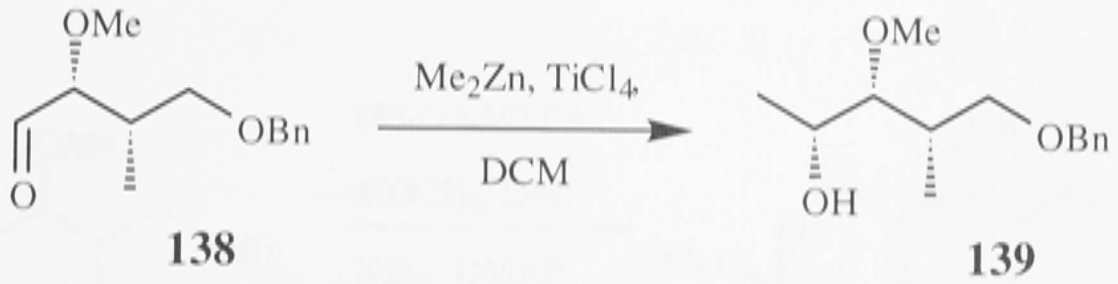
^{13}C NMR (75.5 MHz, $CDCl_3$) δ 203.8 (CH), 138.1 (C), 128.4 (CH), 127.6 (CH), 86.5 (CH), 73.0 (CH_2), 71.0 (CH_2), 58.9 (CH_3), 35.6 (CH), 11.5 (CH_3).

IR (KBr plate, cm^{-1}) 2934, 1732, 1454, 1204, 1091, 738, 699.

Mass Spectrum (70eV) m/z (%) 193 [(M- CHO·)$^+$, 18], 131 (18), 107 (40), 91 (100), 71 (24).

Specific Rotation $[\alpha]_D$ +22.5 (c 2.2).

(2*R*, 3*R*, 4*S*)-3-Methoxy-4-methyl-5-(phenylmethoxy)pentan-2-ol (139)



138 **139**

A magnetically stirred solution of the aldehyde **138** (1.0 g, 4.5 mmol) in dichloromethane (45 ml) was cooled to -78 °C then treated with neat $TiCl_4$ (0.5 ml, 4.5 mmol). After 0.08 h, $(Me)_2Zn$ (2.25 ml of 2.0 M solution in THF, 4.5 mmol) was added. The resulting mixture was stirred at -78 °C for 0.25 h then water was cautiously added at -78 °C and the reaction mixture was allowed to warm to room temperature and extracted with dichloromethane (3 x 100 ml). The combined organic extracts were washed with brine (1 x 25 ml) then dried, filtered and then concentrated under reduced pressure. The oily residue thus obtained was subjected to flash chromatography (silica, 3:7 v/v ethyl acetate/hexane elution) and concentration of the appropriate fractions (R_f = 0.25) afforded the *title compound* ***139*** (0.75 g, 70%) as a clear, colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35-7.31 (complex m, 5H), 4.51 (s, 2H), 3.80 (m, 1H), 3.48 (s, 3H), 3.44 (d, *J* = 6.4 Hz, 1H), 3.07 (m, 1H), 2.60 (br s, 1H), 2.10-2.03 (complex m, 1H), 1.19 (d, *J* = 6.4 Hz, 3H), 0.92 (d, *J* = 7.0 Hz, 3H).

^{13}C NMR (75.5 MHz, $CDCl_3$) δ 138.1 (C), 128.4 (CH), 127.7 (CH), 127.6 (CH), 86.4 (CH), 73.1 (CH_2), 72.6 (CH_2), 67.9 (CH), 61.0 (CH_3), 35.2 (CH), 19.4 (CH_3), 11.8 (CH_3).

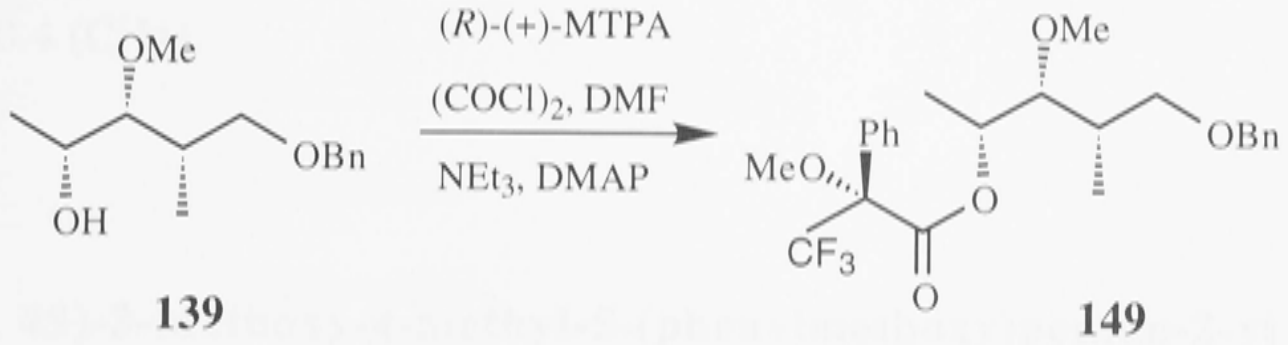
IR (KBr plate, cm^{-1}) 3451, 2972, 1454, 1365, 1090, 737, 698.

Mass Spectrum (70eV) m/z (%) 238 ($M^{+\cdot}$, 11), 193 (21), 131 (20), 107 (13), 91 (100), 71 (24), 57 (17).

HRMS calcd for $C_{14}H_{22}O_3$ ($M^{+\cdot}$), 238.1569. Found: ($M^{+\cdot}$), 238.1560.

Specific Rotation $[\alpha]_D$ +8.6 (c 2.8).

(2*R*, 3*R*, 4*S*)-3-Methoxy-4-methyl-5-(phenylmethoxy)pentan-2-yl (2*R*)-2-Methoxy-2-phenyl-2-trifluoromethylacetate (149)



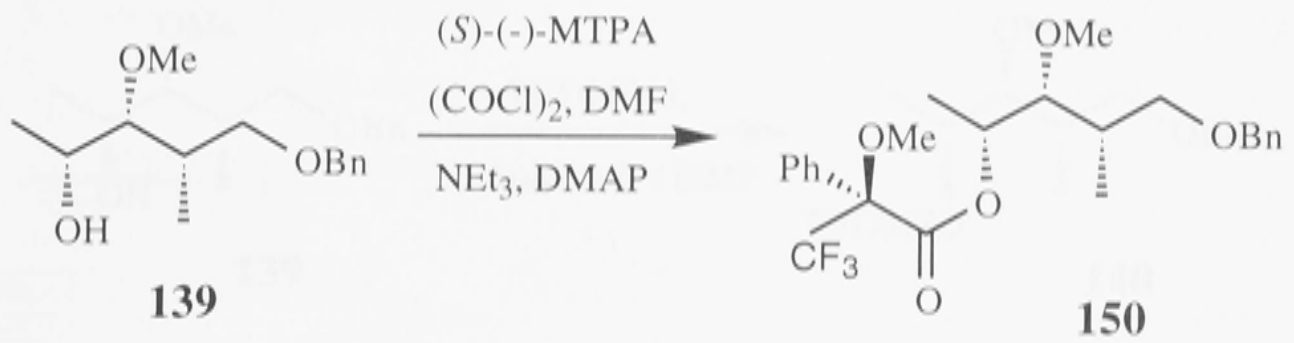
139 **149**

Oxalyl chloride (11.5 µl, 0.13 mmol) followed by *N*, *N*-dimethylformamide (1 drop) was added to a magnetically stirred solution of (*R*)-(+)-MTPA (31 mg, 0.13 mmol) in dichloromethane (0.5 ml) maintained at 0 °C (ice bath) under a nitrogen atmosphere. The reaction mixture was allowed to warm to room temperature, stirred for a further 0.75 h then transferred, *via* cannula, to a chilled (0 °C) and magnetically stirred solution of the alcohol **139** (15 mg, 63 µmol), triethylamine (18.4 µl, 0.13 mmol) and DMAP (2 mg) in dichloromethane (3 ml). The cold bath was removed and the reaction mixture was stirred at room temperature for 16 h. The solution was then partitioned between dichloromethane (10 ml) and $NaHCO_3$ (10 ml of a saturated aqueous solution) and the phases separated. The aqueous layer was extracted with dichloromethane (3 x 10 ml) and the combined organic fractions were washed with brine (1 x 10 ml) then dried, filtered and concentrated under reduced pressure to give a pale-yellow oil. Subjection of the crude material to flash chromatography (silica, 1:4 v/v ethyl acetate/hexane elution) provided, after concentration of the appropriate fractions (R_f = 0.4), the *title compound* ***149*** (19 mg, 65%) as a clear, colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55-7.28 (complex m, 10H), 5.17 (m, 1H), 4.49 (s, 2H), 3.54 (s, 3H), 3.47-3.41 (complex m, 2H), 3.34 (d, *J* = 5.5 Hz, 1H), 3.31 (s, 3H), 2.05-1.90 (complex m, 1H), 1.23 (d, *J* = 6.3 Hz, 3H), 0.87 (d, *J* = 7.1 Hz, 3H).

^{13}C NMR (75.5 MHz, $CDCl_3$) δ 166.1 (C), 138.2 (C), 132.6 (C), 129.4 (CH), 128.4 (CH), 128.3 (CH), 127.8 (CH), 127.7 (CH), 127.2 (CH), 125.3 (C), 122.0 (C), 82.2 (CH), 75.8 (CH), 73.1 (CH_2), 72.3 (CH_2), 60.8 (CH_3), 55.6 (CH_3), 35.0 (CH), 16.7 (CH_3), 10.4 (CH_3).

(2*R*, 3*R*, 4*S*)-3-Methoxy-4-methyl-5-(phenylmethoxy)pentan-2-yl (2*S*)-2-methoxy-2-phenyl-2-trifluoromethylacetate (150)



139 **150**

Oxalyl chloride (11.5 µl, 0.13 mmol) followed by *N*, *N*-dimethylformamide (1 drop) was added to a magnetically stirred solution of (*S*)-(-)-MTPA (31 mg, 0.13 mmol) in dichloromethane (0.5 ml) maintained at 0 °C (ice bath) under a nitrogen atmosphere. The reaction mixture was allowed to warm to room temperature, stirred for a further 0.75 h then transferred, *via* cannula, to a chilled (0 °C) and magnetically stirred solution of the alcohol **139** (15 mg, 63 µmol), triethylamine (18.4 µl, 0.13 mmol) and DMAP (2 mg) in dichloromethane (3 ml). The cold bath was removed and the reaction mixture was stirred at room temperature for 16 h. The solution was then partitioned between dichloromethane (10 ml) and $NaHCO_3$ (10 ml of a saturated aqueous solution) and the phases separated. The aqueous layer was extracted with dichloromethane (3 x 10 ml) and the combined organic fractions were washed with brine (1 x 10 ml) then dried, filtered and concentrated under reduced pressure to give a pale-yellow oil. Subjection of the crude material to flash chromatography (silica, 1:4 v/v ethyl acetate/hexane elution) provided, after concentration of the appropriate fractions (R_f = 0.4), the *title compound **150*** (19 mg, 65%) as a clear, colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58-7.28 (complex m, 10H), 5.20 (m, 1H), 4.46 (s, 2H), 3.60 (s, 3H), 3.40-3.34 (complex m, 2H), 3.26 (dd, *J* = 9.0 and 5.4 Hz, 1H), 3.05 (s, 3H), 1.94-1.90 (complex m, 1H), 1.29 (d, *J* = 6.4 Hz, 3H), 0.84 (d, *J* = 6.9 Hz, 3H).

(2*R*, 3*R*, 4*S*)-2-(*t*-Butyldimethylsiloxy)-3-methoxy-4-methyl-5-(phenyl methoxy)pentane (140)

139 **140**

A magnetically stirred solution of alcohol **139** (1.0 g, 4.2 mmol) and imidazole (0.43 g, 6.3 mmol) in *N*, *N*-dimethylformamide (30 ml) maintained under nitrogen was treated with *t*-butyldimethylsilyl chloride (0.76 g, 5.04 mmol) and the resulting mixture was heated at 60 °C (oil bath) for 3 h. The reaction mixture was then cooled, poured onto crushed ice (25 g) and extracted with ether (3 x 40 ml). The combined organic extracts were dried, filtered and then concentrated under reduced pressure. The oily residue thus obtained was subjected to flash chromatography (silica, 1:4 v/v ethyl acetate/hexane elution) and concentration of the appropriate fractions (R_f = 0.7) then afforded the *title compound **140*** (1.2 g, 80%) as a clear, colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36-7.28 (complex m, 5H), 4.51 (s, 2H), 3.85 (m, 1H), 3.53-3.47 (complex m, 1H), 3.44 (s, 3H), 3.30 (dd, *J* = 9.0 and 6.2 Hz, 1H) 3.10 (dd, *J* = 7.1 and 3.4 Hz, 1H), 2.01-1.98 (complex m, 1H), 1.10 (d, *J* = 6.4 Hz, 3H), 0.90 (s, 9H), 0.86 (d, *J* = 7.0 Hz, 3H), 0.07 (s, 6H).

^{13}C NMR (75.5 MHz, $CDCl_3$) δ 138.6 (C), 128.3 (CH), 127.7 (CH), 127.5 (CH), 85.5 (CH), 73.3 (CH_2), 73.0 (CH_2), 70.5 (CH), 61.0 (CH_3), 35.0 (CH), 26.0 (CH_3), 20.2 (CH_3), 18.1 (C), 10.9 (CH_3), -4.7 (CH_3).

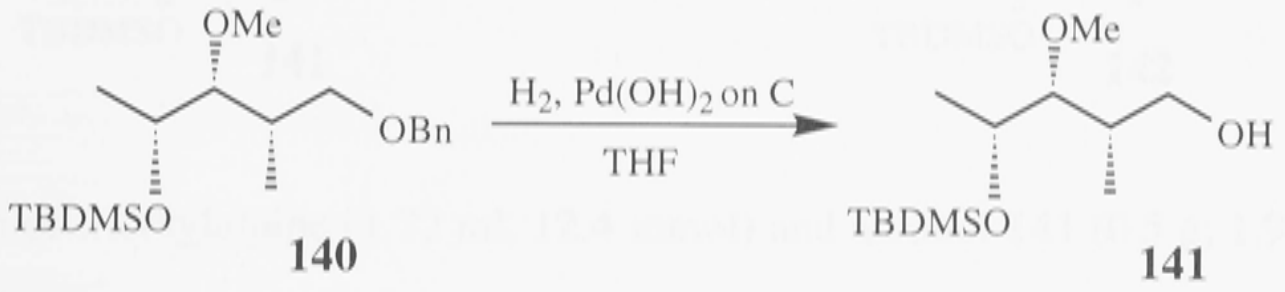
IR (KBr plate, cm^{-1}) 2930, 1455, 1255, 1100, 834, 776.

Mass Spectrum (70eV) m/z (%) 295 [$(M-C_4H_9\cdot)^+$, 6)], 173 (30), 159 (45), 91 (100), 73 (40), 59 (19).

HRMS calcd for $C_{16}H_{27}O_3Si$ $(M-C_4H_9\cdot)^+$, 295.1730. Found: $(M-C_4H_9\cdot)^+$, 295.1730.

Specific Rotation $[\alpha]_D$ +10.4 (c 1.5).

(2*S*, 3*R*, 4*R*)-4-(*t*-Butyldimethylsiloxy)-3-methoxy-2-methylpentan-1-ol (141)



140 **141**

A mixture of compound **140** (1.0 g, 2.84 mmol), palladium hydroxide on carbon (Pearlman's catalyst) (0.15 g) and THF (50 ml) was stirred vigorously under an atmosphere of hydrogen (760 mmHg) for 3 h. The reaction mixture was then filtered through a 2 cm deep pad of TLC grade silica and the filtrate concentrated under reduced pressure. The ensuing oily residue was subjected to flash chromatography (silica, 3:7 v/v ethyl acetate/hexane elution) and concentration of the appropriate fractions ($R_f = 0.5$) then afforded the *title alcohol **141*** (0.7 g, 97%) as a clear, colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 4.12-3.97 (complex m, 1H), 3.60-3.45 (complex m, 2H), 3.43 (s, 3H), 3.00 (br. s, 1H), 2.90 (dd, *J* = 7.2 and 4.9 Hz, 1H), 1.90-1.84 (complex m, 1H), 1.20 (d, *J* = 6.3 Hz, 3H), 0.93 (d, *J* = 6.8 Hz, 3H), 0.91 (s, 9H), 0.12 (s, 6H).

^{13}C NMR (75.5 MHz, $CDCl_3$) δ 88.1 (CH), 69.2 (CH), 66.4 (CH_2), 59.9 (CH_3), 36.9 (CH), 25.8 (CH_3), 18.4 (CH_3), 18.0 (C), 13.2 (CH_3), -4.8 (CH_3), -4.9 (CH_3).

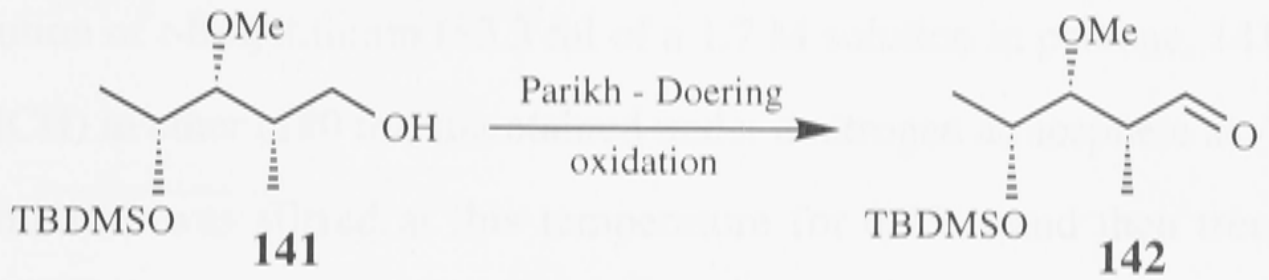
IR (KBr plate, cm^{-1}) 3444, 2961, 2888, 2861, 1463, 1256, 1094, 835, 809, 775, 734.

Mass Spectrum (70eV) m/z (%) 263 ($M+H^+$, 4), 215 (69), 173 (67), 159 (84), 89 (55), 73 (100), 59 (44).

HRMS calcd for $C_{13}H_{30}O_3Si$ ($M+H^+$), 263.2043. Found: ($M+H^+$), 263.2047.

Specific Rotation $[\alpha]_D$ -3.6 (c 1.5).

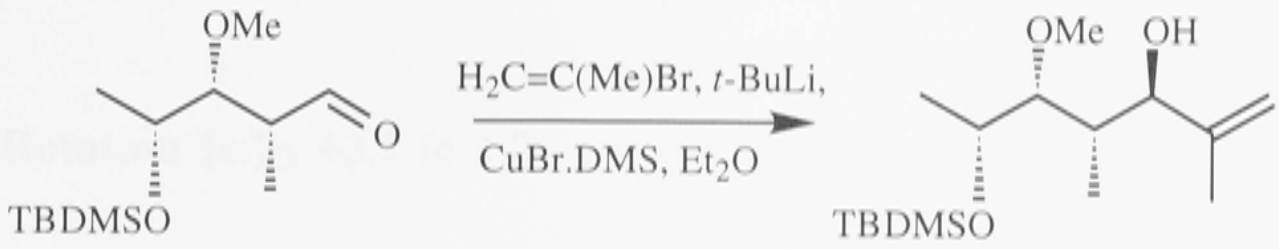
(2*S*, 3*R*, 4*R*)-4-(*t*-Butyldimethylsiloxy)-3-methoxy-2-methylpentanal (142)



141 **142**

A solution of triethylamine (1.72 ml, 12.4 mmol) and alcohol **141** (0.5 g, 1.9 mmol) in dichloromethane (5 ml) was added, dropwise, to a magnetically stirred solution of the sulphur trioxide/pyridine complex (1.2 g, 7.6 mmol) in dimethyl sulfoxide/dichloromethane (15.5 ml of a 3:2 v/v mixture) maintained at 0 °C (ice bath) under a nitrogen atmosphere. The reaction mixture was allowed to warm to room temperature and stirred for a further hour before being quenched with water (25 ml) and extracted with hexane (3 x 25 ml). The combined organic extracts were washed with brine (1 x 15 ml), then dried, filtered and concentrated under reduced pressure. The oily residue thus obtained was subjected to flash chromatography (silica, 1:9 v/v ethyl acetate/hexane elution) and concentration of the appropriate fractions (R_f = 0.4) afforded the *title aldehyde* ***142*** (0.5 g, 94 %) as a clear, colourless oil. Since this aldehyde is highly prone to epimerisation it was immediately subjected to the next step of the reaction sequence.

(3*R*, 4*S*, 5*R*, 6*R*)-6-(*t*-Butyldimethylsiloxy)-2,4-dimethyl-5-methoxy-1-penten-3-ol (143)



142 **143**

Neat 2-bromopropene (6.23 ml, 70.1 mmol) was added, dropwise, to a magnetically stirred solution of *t*-butyllithium (83.3 ml of a 1.7 M solution in pentane, 141.65 mmol, ex ALDRICH) in ether (180 ml) maintained under a nitrogen atmosphere at -78 °C. The resulting mixture was stirred at this temperature for 0.75 h and then treated with a solution of copper(I) bromide-dimethylsulfide complex (7.3 g, 35.6 mmol) in dimethyl sulfide (45 ml). The resulting mixture was stirred at -78 °C for a further 0.5 h and then subjected to addition of a solution of aldehyde **142** (1.35 g, 5.18 mmol) in ether (20 ml). Stirring was continued at this temperature for 0.5 h then the reaction mixture was quenched with NH_4Cl (50 ml of a saturated aqueous solution). The slurry obtained in this manner was warmed to room temperature and extracted with ether (3 x 50 ml). The combined organic extracts were then dried, filtered and concentrated under reduced pressure. The ensuing residue was subjected to flash chromatography (silica, 1.5:8.5 v/v ethyl acetate/hexane elution) and concentration of the appropriate fractions ($R_f = 0.4$) afforded the *title compound* ***143*** (1.10 g, 70%) as a clear, colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.10 (s, 1H), 4.92 (s, 1H), 4.24 (s, 1H), 3.98 (m, 1H), 3.50 (s, 3H), 3.10 (dd, *J* = 6.4 and 4.2 Hz, 1H), 1.86-1.81 (complex m, 1H), 1.68 (s, 3H), 1.14 (d, *J* = 6.5 Hz, 3H), 0.90 (s, 9H), 0.84 (d, *J* = 7.1 Hz, 3H), 0.10 (s, 6H).

^{13}C NMR (75.5 MHz, $CDCl_3$) δ 145.0 (C), 111.2 (CH_2), 89.0 (CH), 77.2 (CH), 70.1 (CH), 60.3 (CH_3), 36.1 (CH_3), 25.9 (CH_3), 19.5 (CH), 19.3 (CH_3), 18.1 (C), 7.3 (CH_3), -4.6 (CH_3), -4.7 (CH_3).

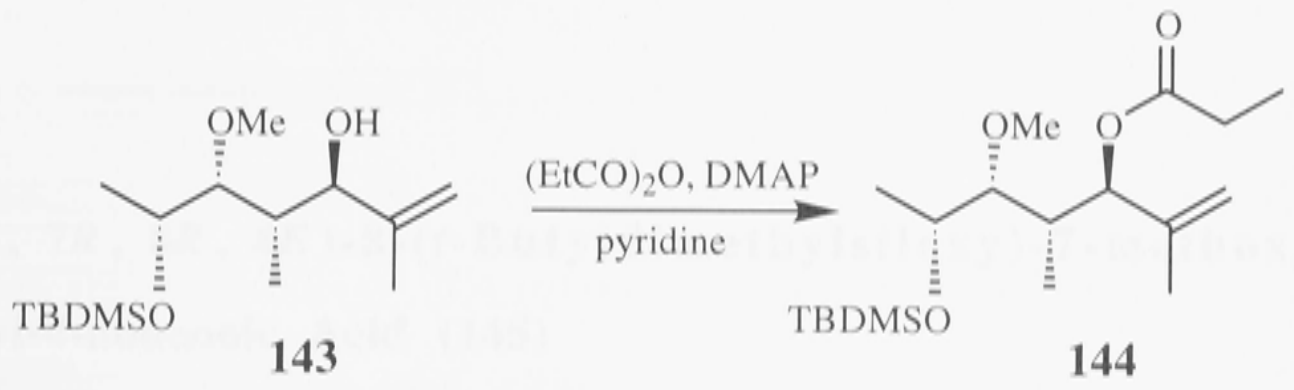
IR (KBr plate, cm^{-1}) 3447, 2931, 1462, 1256, 1093, 988, 900, 835, 776.

Mass Spectrum (70eV) m/z (%) 245 [(M-C_4H_9·)$^+$, 35], 227 (40), 159 (100), 89 (49), 73 (100), 59 (37).

HRMS calcd for $C_{12}H_{25}O_3Si$ (M-C_4H_9·)$^+$, 245.1573. Found: (M-C_4H_9·)$^+$, 245.1570.

Specific Rotation $[\alpha]_D$ +3.2 (c 1.2).

(2'*R*, 3'*S*, 4'*S*, 5'*R*)-6'-(*t*-Butyldimethylsiloxy)-2',4'-dimethyl-5'-methoxy-1'-penten-3'-yl Propionate (144)



143 **144**

A magnetically stirred solution of allylic alcohol **143** (150 mg, 0.5 mmol) in pyridine (4 ml) was treated with propionic anhydride (0.16 ml, 1.2 mmol) and a catalytic amount of 4-(*N*, *N*-dimethylamino)pyridine (2 mg, 0.02 mmol). The resulting mixture was stirred at 18 °C for 16 h then poured onto crushed ice (*ca.* 10 g) and extracted with ether (3 x 25 ml). The combined organic extracts were then washed with HCl (10 ml of a 1 M aqueous solution) and brine (10 ml) before being dried, filtered and concentrated under reduced pressure. Subjection of this material to flash chromatography (silica, 1:4 v/v ethyl acetate/hexane elution) gave, after concentration of the appropriate fractions (R_f = 0.6), the *title ester* ***144*** (160 mg, 90%) as a clear, colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.25 (d, *J* = 8.0 Hz, 1H), 5.02-5.00 (complex m, 2H), 3.91 (m, 1H), 3.43 (s, 3H), 2.92 (dd, *J* = 6.5 and 2.8 Hz, 1H), 2.34 (q, *J* = 7.5 Hz, 2H), 2.06-1.99 (complex m, 1H), 1.70 (s, 3H), 1.14 (t, *J* = 7.6 Hz, 3H), 1.10 (d, *J* = 6.4 Hz, 3H), 0.90 (s, 9H), 0.89 (d, *J* = 8.8 Hz, 3H), 0.08 (s, 6H).

^{13}C NMR (75.5 MHz, $CDCl_3$) δ 173.5 (C), 142.0 (C), 115.5 (CH_2), 85.0 (CH), 79.9 (CH), 70.2 (CH), 60.5 (CH_3), 35.5 (CH_3), 27.9 (CH_2), 26.0 (CH_3), 20.1 (CH), 18.1 (C), 18.0 (CH_3), 9.6 (CH_3), 9.2 (CH_3), -4.6 (CH_3).

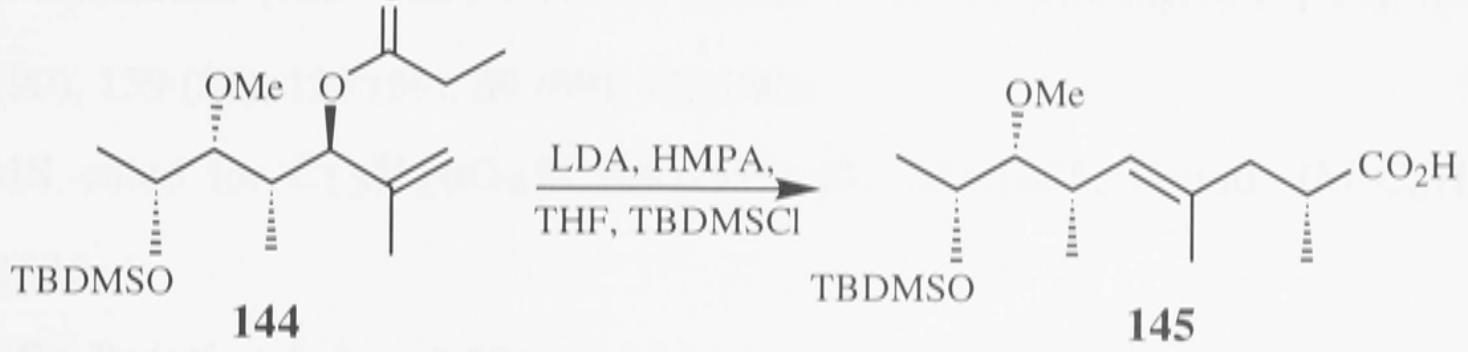
IR (KBr plate, cm^{-1}) 2931, 1741, 1463, 1256, 1184, 1095, 1006, 903, 835, 776.

Mass Spectrum (70eV) m/z (%) 301 [$(M-C_4H_9\cdot)^+$, 4], 227 (14), 159 (70), 89 (62), 73 (84).

HRMS calcd for $C_{15}H_{29}O_4Si$ $(M-C_4H_9\cdot)^+$, 301.1835. Found: $(M-C_4H_9\cdot)^+$, 301.1839.

Specific Rotation $[\alpha]_D$ -22 (c 1.6).

(2*S*, 6*S*, 7*R*, 8*R*, 4*E*)-8-(*t*-Butyldimethylsiloxy)-7-methoxy-2,4,6-trimethyl-4-nonenoic Acid (145)



144 **145**

A magnetically stirred solution of diisopropylamine (27 µl, 0.2 mmol) in THF (1.5 ml) was cooled to -10 °C then treated with *n*-butyllithium (113 µl of a 1.6 M solution in hexane, 0.18 mmol, ex ALDRICH). The resulting mixture was stirred at -10 °C for 0.25 h and then warmed to 18 °C and stirred for a further 0.25 h. After this time the mixture was cooled to -40 °C and THF (0.3 ml) then dry HMPA (0.15 ml) were added. Subsequently the reaction mixture was cooled to -78 °C and a solution of propionate ester **144** (50 mg, 0.14 mmol) was added dropwise over a period of 0.16 h. After 0.25 h TBDMSCl (0.03 g, 0.19 mmol) in THF (0.1 ml) was added rapidly with vigorous stirring. The resulting mixture was stirred at -78 °C for 0.25 h and then allowed to warm to room temperature over a 0.75 h period. After heating to 60 °C for 6 h, the reaction

mixture was diluted with HCl (5 ml of a 1 M aqueous solution) and extracted with ether (3 x 10 ml). The combined organic phases were washed with brine (1 x 10 ml) then dried, filtered and concentrated under reduced pressure. Subjection of this material to flash chromatography (silica, 1.5:8.5 v/v ethyl acetate/hexane elution) gave, after concentration of the appropriate fractions (R_f = 0.2), the *title acid* ***145*** (38 mg, 75%) as a clear, colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.20 (d, *J* = 9.3 Hz, 1H), 3.83 (t, *J* = 6.7 Hz, 1H), 3.43 (s, 3H), 2.80 (t, *J* = 5.4 Hz, 1H), 2.65-2.53 (complex m, 2H), 2.41-2.35 (complex m, 1H), 2.08-2.01 (complex m, 1H), 1.61 (s, 3H), 1.13 (d, *J* = 6.7 Hz, 3H), 1.11 (d, *J* = 6.7 Hz, 3H), 1.00 (d, *J* = 6.7 Hz, 3H), 0.90 (s, 9H), 0.06 (s, 6H).

^{13}C NMR (75.5 MHz, $CDCl_3$) δ 182.4 (C), 131.8 (CH), 130.1 (C), 89.7 (CH), 70.1 (CH), 60.8 (CH_3), 43.7 (CH_2), 37.9 (CH), 33.8 (CH), 25.9 (CH_3), 20.1 (CH_3), 18.1 (C), 16.4 (CH_3), 15.8 (CH_3), 15.4 (CH_3), -4.56 (CH_3), -4.6 (CH_3).

IR (KBr plate, cm^{-1}) 2958, 2931, 1709, 1254, 1093, 834, 776.

Mass Spectrum (70eV) m/z (%) 358 ($M+H^+$, 3), 301 [$(M-C_4H_9\cdot)^+$, 14], 225 (8), 203 (90), 159 (57), 133 (59), 89 (69), 73 (100).

HRMS calcd for $C_{15}H_{29}O_4Si$ $(M-C_4H_9\cdot)^+$, 301.1835. Found: $(M-C_4H_9\cdot)^+$, 301.1836.

Specific Rotation $[\alpha]_D$ +5.82 (c 2.15).

(2*S*, 6*S*, 7*R*, 8*R*, 5*E*)-8-(*t*-Butyldimethylsiloxy)-7-methoxy-2,4,6-trimethyl-4-nonen-1-ol (146)

145 **146**

$LiAlH_4$ (0.28 ml of a 1 M solution in THF, 0.28 mmol, ex ALDRICH) was added, dropwise, to a magnetically stirred solution of the acid **145** (100 mg, 0.28 mmol) in ether

(4 ml) maintained under a nitrogen atmosphere at 0 °C. The resulting mixture was allowed to warm to room temperature and stirred for a further 1 h then cooled and treated sequentially with water (2 ml), NaOH (2 ml of a 10% (w/v) aqueous solution) and water (5 ml). The resulting precipitate was filtered off and the solids thus retained were washed successively with ether (1 x 50 ml) and hot chloroform (1 x 25 ml). The combined filtrates were then dried, filtered and concentrated under reduced pressure to give a light -yellow oil. Subjection of this material to flash chromatography (silica, 1:4 v/v ethyl acetate/hexane elution) gave, after concentration of the appropriate fractions (R_f = 0.4), the *title alcohol* ***146*** (63 mg, 66%) as a clear, colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.20 (d, *J* = 9.2 Hz, 1H), 3.83 (m, 1H), 3.53-3.47 (complex m, 2H), 3.44 (s, 3H), 2.80 (t, *J* = 5.7 Hz, 1H), 2.58-2.55 (complex m, 1H), 2.10-2.03 (complex m, 1H), 1.87-1.80 (complex m, 2H), 1.62 (s, 3H), 1.12 (d, *J* = 6.2 Hz, 3H), 0.92 (d, *J* = 6.7 Hz, 3H), 0.87 (d, *J* = 6.9 Hz, 3H), 0.90 (s, 9H), 0.06 (s, 6H).

^{13}C NMR (75.5 MHz, $CDCl_3$) δ 132.0 (C), 131.0 (CH), 89.7 (CH), 70.1 (CH), 68.6 (CH_2), 60.9 (CH_3), 44.4 (CH_2), 33.72 (CH), 33.69 (CH), 26.0 (CH_3), 20.1 (CH_3), 18.1 (C), 16.9 (CH_3), 16.1 (CH_3), 15.4 (CH_3), -4.56 (CH_3), -4.60 (CH_3).

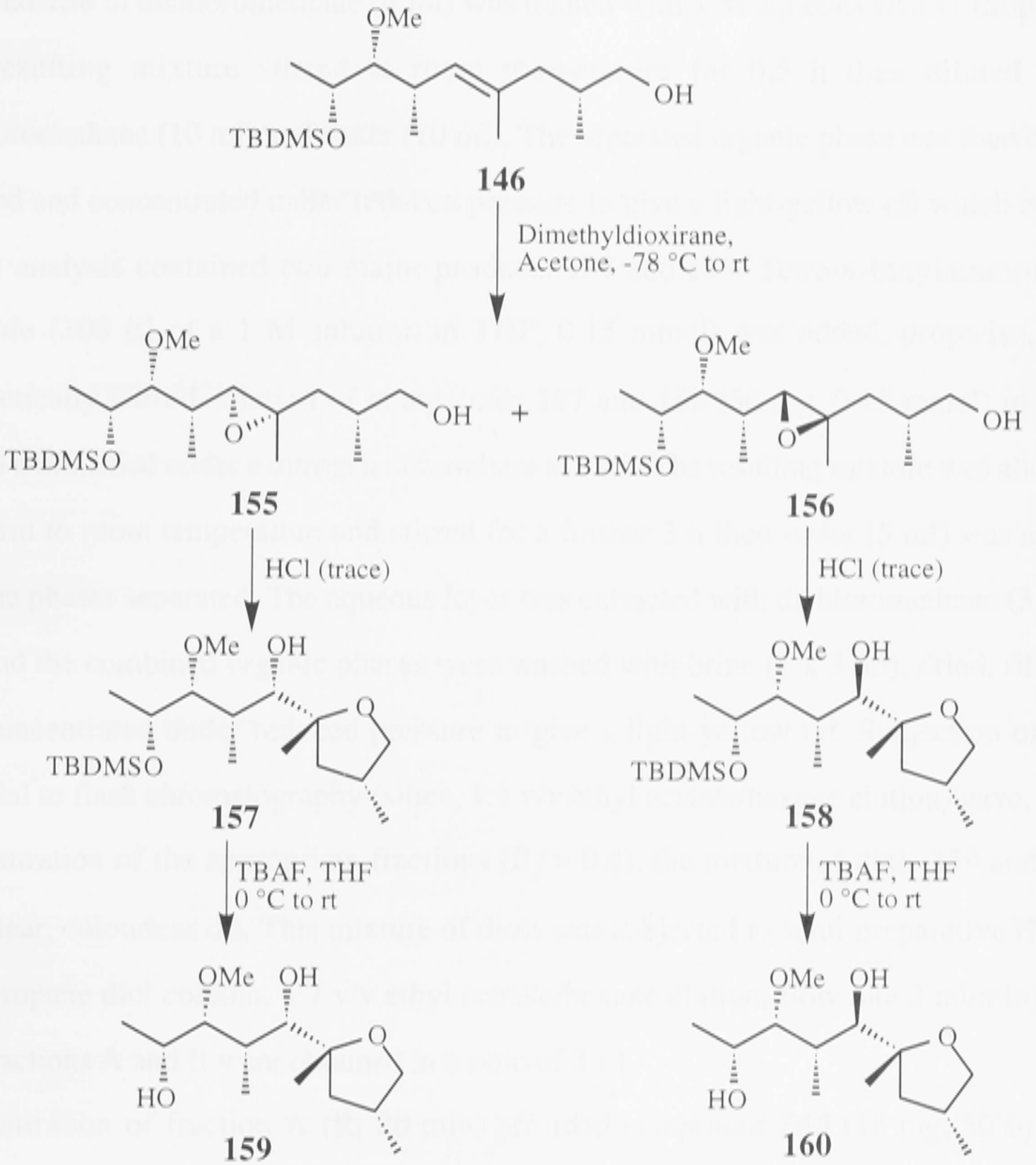
IR (KBr plate, cm^{-1}) 3337, 2957, 2930, 1255, 1093, 834, 775.

Mass Spectrum (70eV) m/z (%) 344 ($M^{+\cdot}$, 9), 312 (14), 287 [$(M-C_4H_9\cdot)^+$, 17], 255 [$(M-C_4H_9-MeOH\cdot)^+$, 12], 203 (82), 159 (58), 133 (56), 89 (75), 73 (100), 59 (42).

HRMS calcd for $C_{19}H_{40}O_3Si$ ($M^{+\cdot}$), 344.2747. Found: ($M^{+\cdot}$), 344.2750.

Specific Rotation $[\alpha]_D$ +6.4 (c 1.6).

[(2'*R*, 4'*R*)-(Dimethyl-tetrahydrofuran-2'-yl)]-(1*R*, 2*R*, 3*R*, 4*R*)-3-methoxy-2-methyl-1,4-diol 159 and [(2'*R*, 4'*R*)-(Dimethyl-tetrahydrofuran-2'-yl)]-(1*S*, 2*R*, 3*R*, 4*R*)-3-methoxy-2-methyl-1,4-diol (160)



Dimethyldioxirane (2.2 ml of a 0.1 M solution in acetone, 0.22 mmol) was added to a magnetically stirred solution of alcohol **146** (75 mg, 0.22 mmol) in anhydrous acetone (1 ml) maintained under a nitrogen atmosphere at -78 °C. The resulting mixture was stirred for 1 h at -78 °C and then allowed to warm to room temperature and concentrated under reduced pressure. TLC analysis of the yellow oil thus obtained (1:4 v/v ethyl

acetate/hexane elution on silical gel) revealed two spots of R_f 0.2 and 0.25 which are attributed to the presence of the diastereoisomeric epoxides **155** and **156**. However, the instability of these compounds prompted their immediate subjection to acid-catalysed cyclisation so as to form tetrahydrofurans **157** and **158**. Thus, a solution of epoxides **155** and **156** in dichloromethane (4 ml) was treated with 1 M aqueous HCl (1 drop) and the resulting mixture stirred at room temperature for 0.5 h then diluted with dichloromethane (10 ml) and water (10 ml). The separated organic phase was then dried, filtered and concentrated under reduced pressure to give a light-yellow oil which by ^{1}H NMR analysis contained two major products **157** and **158**. Tetra-*n*-butylammonium fluoride (308 µl of a 1 M solution in THF, 0.15 mmol) was added, dropwise, to a magnetically stirred solution of compounds **157** and **158** (56 mg, 0.15 mmol) in THF (2 ml) maintained under a nitrogen atmosphere at 0 °C. The resulting mixture was allowed to warm to room temperature and stirred for a further 3 h then water (5 ml) was added and the phases separated. The aqueous layer was extracted with dichloromethane (3 x 10 ml) and the combined organic phases were washed with brine (1 x 5 ml), dried, filtered and concentrated under reduced pressure to give a light-yellow oil. Subjection of this material to flash chromatography (silica, 1:1 v/v ethyl acetate/hexane elution) gave, after concentration of the appropriate fractions (R_f = 0.4), the mixture of diols **159** and **160** as a clear, colourless oil. This mixture of diols was subjected to semi-preparative HPLC (2,3-propane diol column, 3:7 v/v ethyl acetate/hexane elution, flow rate 2 ml/min) and two fractions A and B were obtained in a ratio of 3 : 1.

Concentration of fraction A (R_t 20 min) afforded *compound **160*** (18 mg, 50%) as a clear, colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 3.94 (t, *J* = 8.0 Hz, 2H), 3.81 (s, 1H), 3.50 (s, 3H), 3.30 (t, *J* = 8.9 Hz, 1H), 2.88 (dd, *J* = 5.1 and 1.8 Hz, 1H), 2.50-2.30 (complex m, 4H), 1.80-1.70 (complex m, 1H), 1.60-1.50 (complex m, 1H), 1.26 (d, *J* = 6.6 Hz, 3H), 1.23 (s, 3H), 1.04 (d, *J* = 6.6 Hz, 3H), 0.95 (d, *J* = 7.2 Hz, 3H).

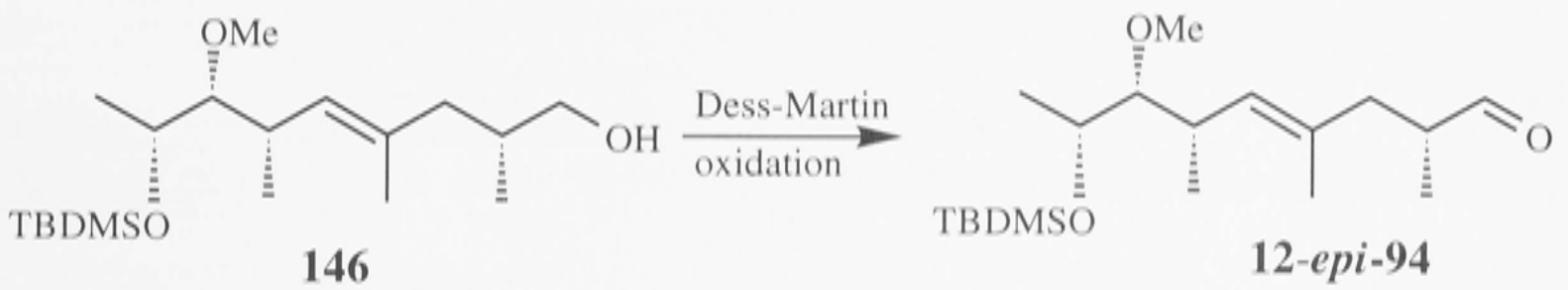
^{13}C NMR (75.5 MHz, $CDCl_3$) δ 87.5 (CH), 86.2 (C), 73.3 (CH_2), 72.8 (CH), 65.8 (CH), 58.6 (CH_3), 42.9 (CH_2), 35.2 (CH), 33.0 (CH), 24.1 (CH_3), 21.1 (CH_3), 17.4 (CH_3), 10.1 (CH_3).

Concentration of fraction B (R_t 21 min) afforded *compound **159*** (7 mg, 16%) as a clear, colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 4.05-3.90 (complex m, 1H), 3.90-3.80 (complex m, 1H), 3.57 (s, 3H), 3.38-3.20 (complex m, 2H), 2.50-2.20 (complex m, 2H), 1.80-1.70 (complex m, 2H), 1.64-1.60 (complex m, 1H), 1.21 (s, 3H), 1.20 (d, J = 5.6 Hz, 3H), 1.04 (d, J = 6.5 Hz, 3H), 0.95 (d, J = 6.9 Hz, 3H).

^{13}C NMR (75.5 MHz, $CDCl_3$) δ 87.8 (CH), 86.2 (C), 75.2 (CH_2), 72.8 (CH), 65.3 (CH), 59.2 (CH_3), 44.0 (CH_2), 35.2 (CH), 33.7 (CH), 23.1 (CH_3), 20.4 (CH_3), 16.2 (CH_3), 14.1 (CH_3).

(2*S*, 6*S*, 7*R*, 8*R*, 5*E*)-8-(*t*-Butyldimethylsiloxy)-7-methoxy-2,4,6-trimethyl-4-nonenal (12-*epi*-94)



146 **12-*epi*-94**

The Dess-Martin periodinane (90 mg, 0.22 mmol) was added to a magnetically stirred solution of alcohol **146** (51 mg, 0.15 mmol) in dichloromethane (1.5 ml) maintained at 18 °C under a nitrogen atmosphere. Stirring was continued for 0.75 h then the reaction mixture was diluted with diethyl ether (2 ml), $NaHCO_3$ (2 ml of a saturated aqueous solution) and $Na_2S_2O_3$ (2 ml of a 1 M aqueous solution) and stirring was continued until two clear layers were observed. The separated aqueous layer was extracted with diethyl ether (2 x 15 ml) and the combined organic fractions were dried, filtered and concentrated under reduced pressure to give a light-yellow oil. Subjection of this material to flash

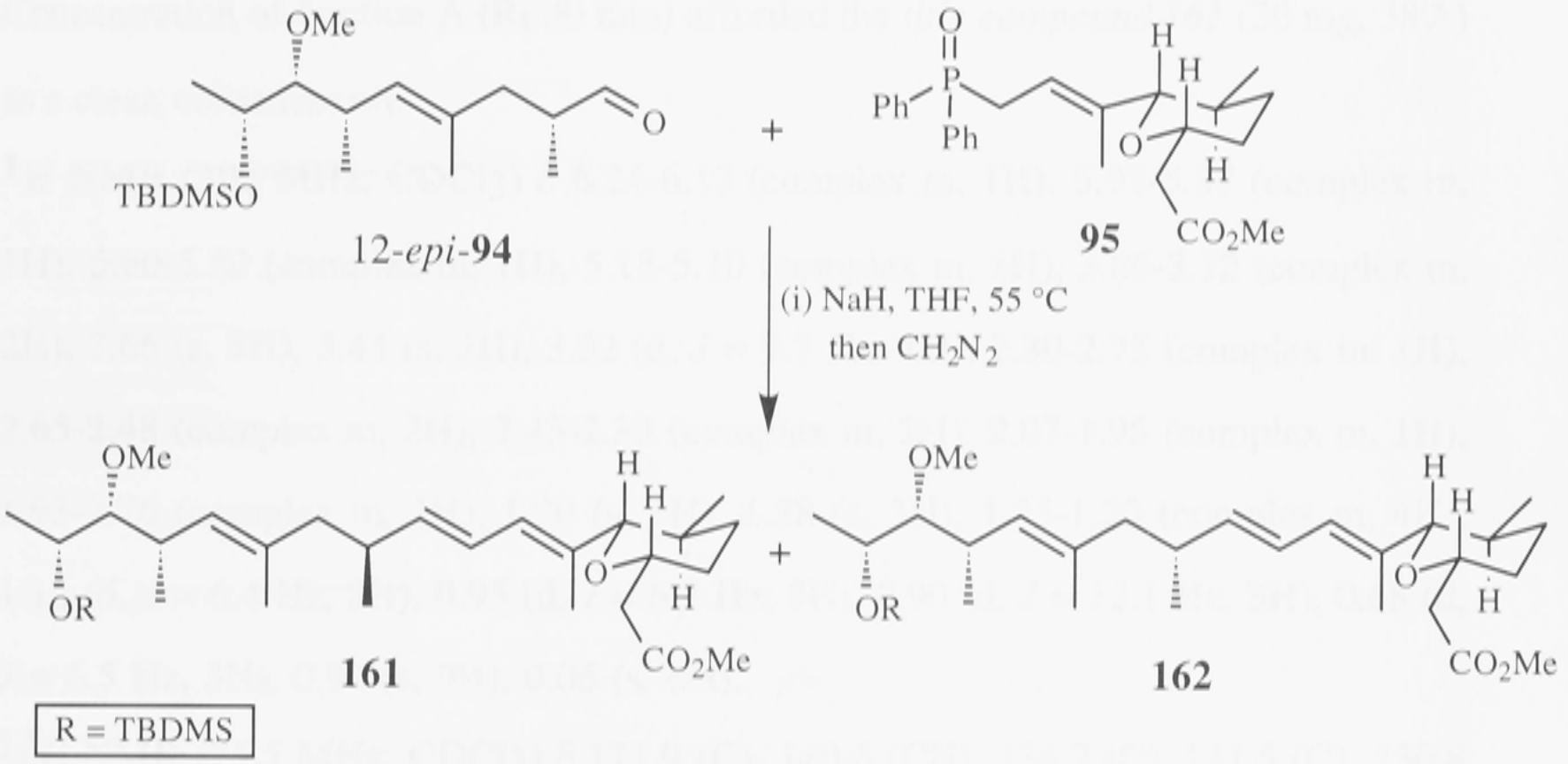
chromatography (silica, 1:4 v/v ethyl acetate/hexane elution) gave, after concentration of the appropriate fractions (R_f = 0.7), the *title compound 12*-epi-***94*** (31 mg, 62%) as a clear, colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.61 (d, *J* = 2.3 Hz, 1H), 5.22 (d, *J* = 9.3 Hz, 1H), 3.83 (m, 1H), 3.43 (s, 3H), 2.80 (t, *J* = 5.5 Hz, 1H), 2.59-2.51 (complex m, 1H), 2.50-2.38 (complex m, 1H), 2.04-1.94 (complex m, 1H), 1.61 (s, 3H), 1.11 (d, *J* = 6.7 Hz, 3H), 1.04 (d, *J* = 7.0 Hz, 3H), 0.91 (d, *J* = 6.6 Hz, 3H), 0.90 (s, 9H), 0.06 (s, 6H).

This compound is unstable and was not, therefore, subjected to full characterisation but, rather, immediately subjected to the next step of the reaction sequence.

5.4 Experimental Procedures Associated with Work Described in Chapter Four

Methyl (2*S*, 3*S*, 6*R*)-{[1*E*, 3*E*, 7*E*, 11*R*, 10*R*, 9*R*, 5*S*)-11-*t*-Butyldimethylsiloxy-10-methoxy-1,5,7,9-tetramethyldodeca-1,3,7-trienyl]-3-methyloxan-6-yl}ethanoate (161) and Methyl (2*S*, 3*S*, 6*R*)-{[1*E*, 3*E*, 7*E*, 11*R*, 10*R*, 9*R*, 5*R*)-11-*t*-Butyldimethylsiloxy-10-methoxy-1,5,7,9-tetramethyldodeca-1,3,7-trienyl]-3-methyloxan-6-yl}ethanoate (162)



A solution of phosphine oxide **95** (62 mg, 0.15 mmol) in THF (2 ml) was added, *via* syringe, to a magnetically stirred suspension of NaH (60 mg of a 35% w/w dispersion in mineral oil, 1.5 mmol) in anhydrous THF (10 ml) maintained under a nitrogen atmosphere. The resulting mixture was stirred at room temperature for 0.5 h and then treated with compound 12-*epi*-**94** (50 mg, 0.15 mmol). The reaction mixture was then heated to 55 °C and stirring was continued for 2 h. The cooled reaction mixture was then poured onto crushed ice and the resulting melt was acidified with concentrated HCl to pH~2-3. The mixture thus obtained was extracted with ether (3 x 20 ml) and the combined organic extracts were then dried, filtered and concentrated under reduced pressure to give a clear, colourless oil. This material was treated with diazomethane (8 ml

of a 0.35 M solution in ether, 2.8 mmol) at 0 °C and the resulting mixture was allowed to warm to room temperature and left stirring for 0.5 h. The light-yellow solution thus obtained was poured into water (10 ml) and extracted with ether (3 x 10 ml). The combined organic extracts were then dried, filtered and concentrated under reduced pressure to give a pale-yellow oil. This material was subjected to semi-preparative HPLC (2,3-propane diol column, 1:99 v/v MTBE/hexane elution, flow rate 2 ml/min) and two fractions A and B were obtained in a ratio of 1.5:1.

Concentration of fraction A (R_t 30 min) afforded the *title compound* ***161*** (30 mg, 38%) as a clear, colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.24-6.13 (complex m, 1H), 5.92-5.87 (complex m, 1H), 5.60-5.50 (complex m, 1H), 5.15-5.10 (complex m, 1H), 3.86-3.72 (complex m, 2H), 3.66 (s, 3H), 3.44 (s, 3H), 3.32 (d, *J* = 9.7 Hz, 1H), 2.80-2.75 (complex m, 1H), 2.65-2.48 (complex m, 2H), 2.43-2.33 (complex m, 2H), 2.07-1.95 (complex m, 1H), 1.93-1.76 (complex m, 2H), 1.70 (s, 3H), 1.58 (s, 3H), 1.55-1.20 (complex m, 4H), 1.12 (d, *J* = 6.4 Hz, 3H), 0.95 (d, *J* = 6.7 Hz, 3H), 0.90 (d, *J* = 12.1 Hz, 3H), 0.68 (d, *J* = 6.5 Hz, 3H), 0.90 (s, 9H), 0.06 (s, 6H).

^{13}C NMR (75.5 MHz, $CDCl_3$) δ 171.9 (C), 140.6 (CH), 134.2 (C), 131.5 (C), 130.8 (CH), 128.5 (CH), 123.8 (CH), 90.6 (CH), 89.8 (CH), 73.8 (CH), 70.1 (CH), 61.0 (CH_3), 51.6 (CH_3), 47.5 (CH_2), 41.3 (CH_2), 35.1 (CH), 33.7 (CH), 32.3 (CH_2), 32.1 (CH), 31.7 (CH_2), 26.0 (CH_3), 20.2 (CH_3), 20.1 (CH_3), 18.1 (C), 17.7 (CH_3), 16.2, (CH_3), 15.5 (CH_3), 12.0 (CH_3), -4.60 (CH_3).

IR (KBr plate, cm^{-1}) 2954, 1743, 1455, 1254, 1197, 1067, 834, 775.

Mass Spectrum (70eV) m/z (%) 550 ($M^{+\cdot}$, 22), 493 [$(M-C_4H_9\cdot)^+$, 2], 449 (7), 347 (6), 265 (98), 203 (100), 159 (40), 133 (32), 95 (48), 73 (70), 59 (16).

HRMS calcd for $C_{32}H_{58}O_5Si$ ($M^{+\cdot}$), 550.4054. Found: ($M^{+\cdot}$), 550.4060.

Specific Rotation $[\alpha]_D$ +0.35 (c 2.3)

UV (λmax) 239 nm (ε 21 080).

Concentration of fraction B (R_t 26 min) afforded the compound **162** (20 mg, 25%) as a clear, colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.24-6.10 (complex m, 1H), 5.90 (d, *J* = 11.0 Hz, 1H), 5.60 (dd, *J* = 15.1 and 7.3 Hz, 1H), 5.13 (d, *J* = 9.5 Hz, 1H), 3.84-3.74 (complex m, 2H), 3.66 (s, 3H), 3.43 (s, 3H), 3.31 (d, *J* = 9.8 Hz, 1H), 2.80-2.74 (complex m, 1H), 2.64-2.51 (complex m, 2H), 2.44-2.36 (complex m, 2H), 2.07-2.00 (complex m, 1H), 1.95-1.81 (complex m, 2H), 1.70 (s, 3H), 1.58 (s, 3H), 1.57-1.20 (complex m, 4H), 1.12 (d, *J* = 6.4 Hz, 3H), 0.93 (d, *J* = 3.9 Hz, 3H), 0.91 (d, *J* = 4.1 Hz, 3H), 0.69 (d, *J* = 6.6 Hz, 3H), 0.90 (s, 9H), 0.06 (s, 6H).

^{13}C NMR (75.5 MHz, $CDCl_3$) δ 171.9 (C), 140.7 (CH), 134.2 (C), 131.5 (C), 130.9 (CH), 128.4 (CH), 123.7 (CH), 90.8 (CH), 89.7 (CH), 73.8 (CH), 70.1 (CH), 60.9 (CH_3), 51.5 (CH_3), 47.5 (CH_2), 41.3 (CH_2), 34.8 (CH), 33.7 (CH), 32.3 (CH_2), 32.3 (CH_2), 32.2 (CH), 31.6 (CH_2), 26.0 (CH_3), 20.2 (CH_3), 19.5 (CH_3), 18.1 (C), 17.7 (CH_3), 16.2, (CH_3), 15.5 (CH_3), 12.3 (CH_3), -4.60 (CH_3).

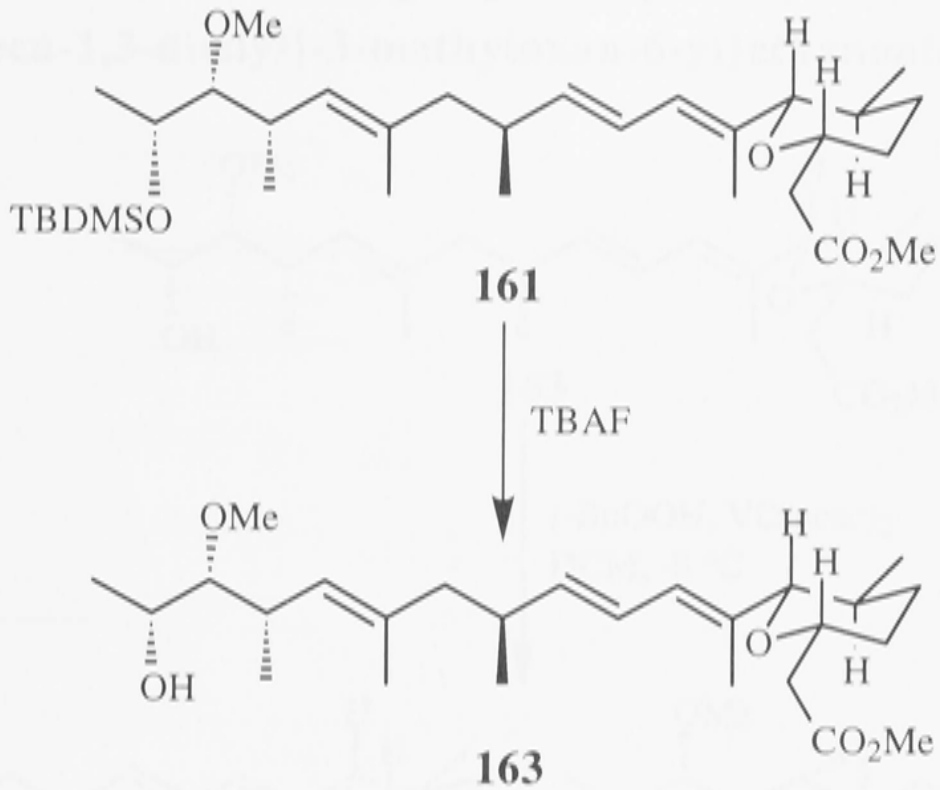
IR (KBr plate, cm^{-1}) 2954, 1743, 1455, 1254, 1197, 1067, 834, 775.

Mass Spectrum (70eV) m/z (%) 550 ($M^{+\cdot}$, 40), 493 [$(M-C_4H_9\cdot)^+$, 2], 449 (11), 347 (10), 265 (90), 203 (100), 159 (50), 133 (42), 95 (56), 73 (74), 59 (22).

HRMS calcd for $C_{32}H_{58}O_5Si$ ($M^{+\cdot}$), 550.4054. Found: ($M^{+\cdot}$), 550.4049.

UV (λmax) 239 nm (ε 21 080).

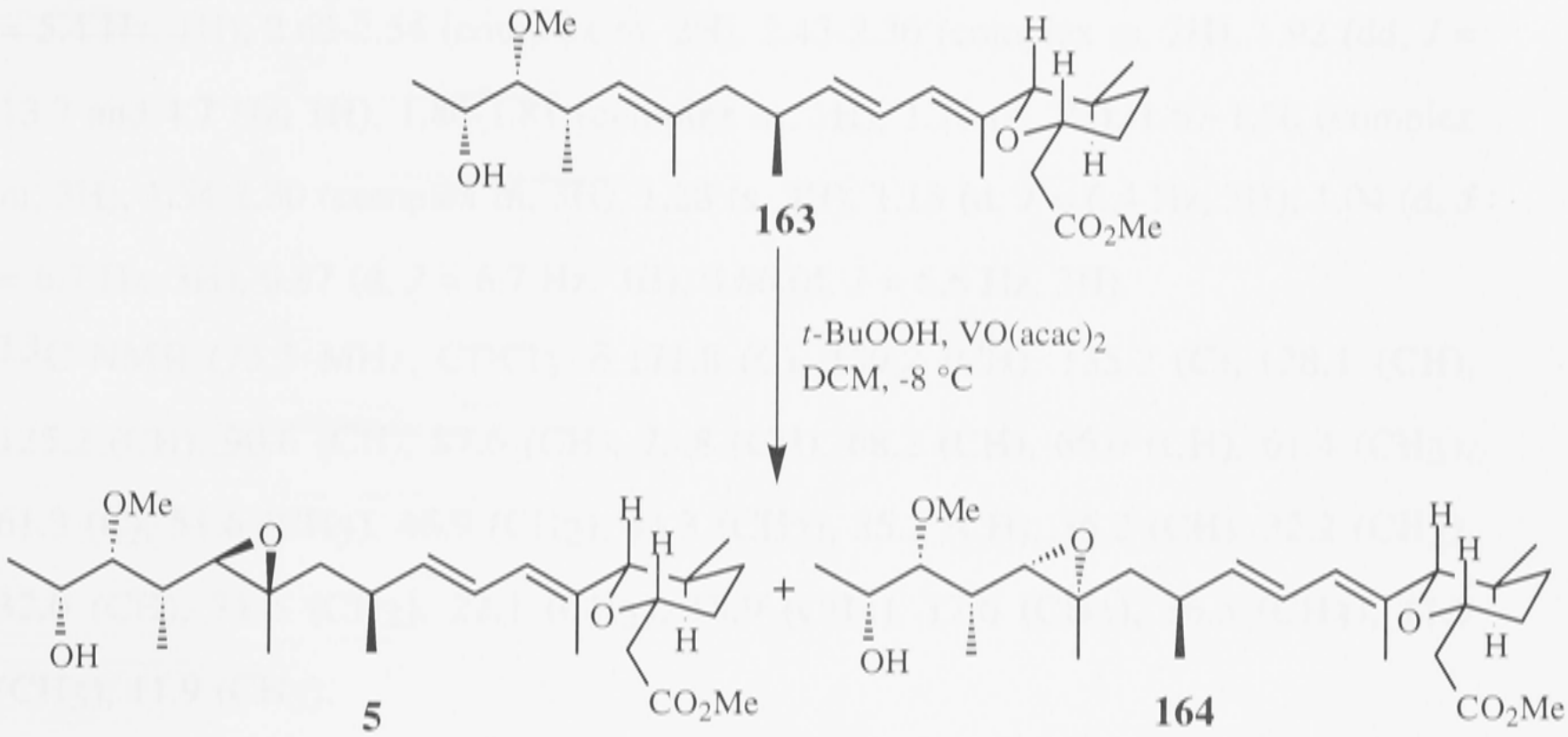
Methyl (2*S*, 3*S*, 6*R*)-{[1*E*, 3*E*, 7*E*, 11*R*, 10*R*, 9*R*, 5*S*)-11-Hydroxy-10-methoxy-1,5,7,9-tetramethyldodeca-1,3,7-trienyl]-3-methyloxan-6-yl}ethanoate (163)



Tetra-*n*-butylammonium fluoride (61 µl of a 1 M solution in THF, 61 µmol) was added, dropwise, to a magnetically stirred solution of the compound **161** (23 mg, 0.04 mmol) in THF (2 ml) maintained at 0 °C under a nitrogen atmosphere. The resulting mixture was allowed to warm to room temperature and stirred for a further 6 h then water (5 ml) was added and the phases separated. The aqueous layer was extracted with dichloromethane (3 x 10 ml) and the combined organic phases were washed with brine (1 x 5 ml) then dried, filtered and concentrated under reduced pressure to give a light-yellow oil. Subjection of this material to flash chromatography (silica, 3:7 v/v ethyl acetate/hexane elution) gave, after concentration of the appropriate fractions (R_f = 0.4), the *title compound* ***163*** (12 mg, 68%) as a clear, colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.23-6.13 (complex m, 1H), 5.92-5.88 (complex m, 1H), 5.60-5.50 (complex m, 1H), 5.00-4.95 (complex m, 1H), 3.80-3.70 (complex m, 2H), 3.66 (s, 3H), 3.50 (s, 3H), 3.32 (d, *J* = 9.7 Hz, 1H), 2.72-2.56 (complex m, 3H), 2.43-2.36 (complex m, 2H), 2.10-1.80 (complex m, 3H), 1.70 (s, 3H), 1.61 (s, 3H), 1.57-1.23 (complex m, 4H), 1.19 (d, *J* = 6.5 Hz, 3H), 0.95 (d, *J* = 6.5 Hz, 3H), 0.70 (d, *J* = 4.5 Hz, 3H), 0.68 (d, *J* = 4.5 Hz, 3H).

Methyl (2*S*, 3*S*, 6*R*)-{[1*E*, 3*E*, 11*R*, 10*R*, 9*R*, 8*R*, 7*R*, 5*S*)-7,8-Epoxy-11-hydroxy-10-methoxy-1,5,7,9-tetramethyldodeca-1,3-dienyl]-3-methyloxan-6-yl}ethanoate (163) and Methyl (2*S*, 3*S*, 6*R*)-{[1*E*, 3*E*, 11*R*, 10*R*, 9*R*, 8*S*, 7*S*, 5*S*)-7,8-Epoxy-11-hydroxy-10-methoxy-1,5,7,9-tetramethyldodeca-1,3-dienyl]-3-methyloxan-6-yl}ethanoate (164)



A magnetically stirred solution of compound **163** (20 mg, 0.047 mmol) in anhydrous dichloromethane (0.4 ml) maintained at -8 °C using cryobath under nitrogen atmosphere was treated with vanadyl bis(acetylacetonate) (0.12 mg, 0.5 µmol) followed by the slow addition of a solution of *tert*-butyl hydroperoxide (TBHP) (28 µl of a 5.0 M solution in decane, 0.14 mmol) in anhydrous dichloromethane (0.4 ml) *via* a syringe pump over 48 h. After the complete addition of the stoichiometric oxidant the colourless solution was allowed to stir for a further 24 h at -8 °C. After this time the mixture was diluted with ether (5 ml) and water (5 ml) and the layers shaken well and then separated. The aqueous phase was then extracted with dichloromethane (3 x 5 ml) and the combined organic extracts were washed with brine (1 x 5 ml), dried, filtered under reduced pressure. This material was subjected to semi-preparative HPLC (2,3-propane diol column, 1.5:8.5 v/v MTBE/hexane elution, flow rate 1 ml/min) and two fractions A and B were obtained.

Concentration of fraction A (R_t 35 min) afforded compound **5**[9] (13 mg, 63%) as a clear, colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.23 (dd, *J* = 15.3 and 10.56 Hz, 1H), 5.90 (d, *J* = 10.9 Hz, 1H), 5.43 (dd, *J* = 14.9 and 8.8 Hz, 1H), 3.86-3.77 (complex m, 1H), 3.76-3.75 (complex m, 1H), 3.66 (s, 3H), 3.54 (s, 3H), 3.32 (d, *J* = 9.8 Hz, 1H), 2.97 (t, *J* = 5.4 Hz, 1H), 2.63-2.54 (complex m, 2H), 2.43-2.36 (complex m, 2H), 1.92 (dd, *J* = 13.7 and 4.7 Hz, 1H), 1.86-1.81 (complex m, 1H), 1.70 (s, 3H), 1.67-1.56 (complex m, 3H), 1.54-1.30 (complex m, 3H), 1.28 (s, 3H), 1.18 (d, *J* = 6.4 Hz, 3H), 1.04 (d, *J* = 6.7 Hz, 3H), 0.87 (d, *J* = 6.7 Hz, 3H), 0.66 (d, *J* = 6.6 Hz, 3H).

^{13}C NMR (75.5 MHz, $CDCl_3$) δ 171.8 (C), 139.2 (CH), 135.2 (C), 128.1 (CH), 125.2 (CH), 90.6 (CH), 87.6 (CH), 73.8 (CH), 68.2 (CH), 66.0 (CH), 61.4 (CH_3), 61.3 (C), 51.6 (CH_3), 46.9 (CH_2), 41.3 (CH_2), 35.3 (CH), 35.2 (CH), 32.2 (CH_2), 32.0 (CH), 31.6 (CH_2), 22.1 (CH_3), 18.9 (CH_3), 17.6 (CH_3), 16.5 (CH_3), 11.9 (CH_3), 11.9 (CH_3).

IR (KBr plate, cm^{-1}) 3454, 2917, 2849, 1738, 1455, 1068.

Mass Spectrum (70eV) m/z (%) 452 ($M^{+\cdot}$, 10), 434 (4), 351 (4), 305 (4), 278 (12), 265 (12), 237 (5), 197 (14), 169 (58), 143 (34), 129 (90), 100 (80), 69 (100).

HRMS calcd for $C_{26}H_{44}O_6$ ($M^{+\cdot}$), 452.3138. Found: ($M^{+\cdot}$), 452.3137.

Specific Rotation $[\alpha]_D$ +1.3 (c 0.2), {lit.[9] $[\alpha]_D$ = +0.9 (c 0.7)}

UV (λmax) 246 nm (ε 21 000).

Concentration of fraction B (R_t 36 min) afforded trace amounts (< 0.5 mg) of a light-yellow oil which is tentatively identified as *compound **164***, the diastereoisomer of herboxidiene methyl ester.

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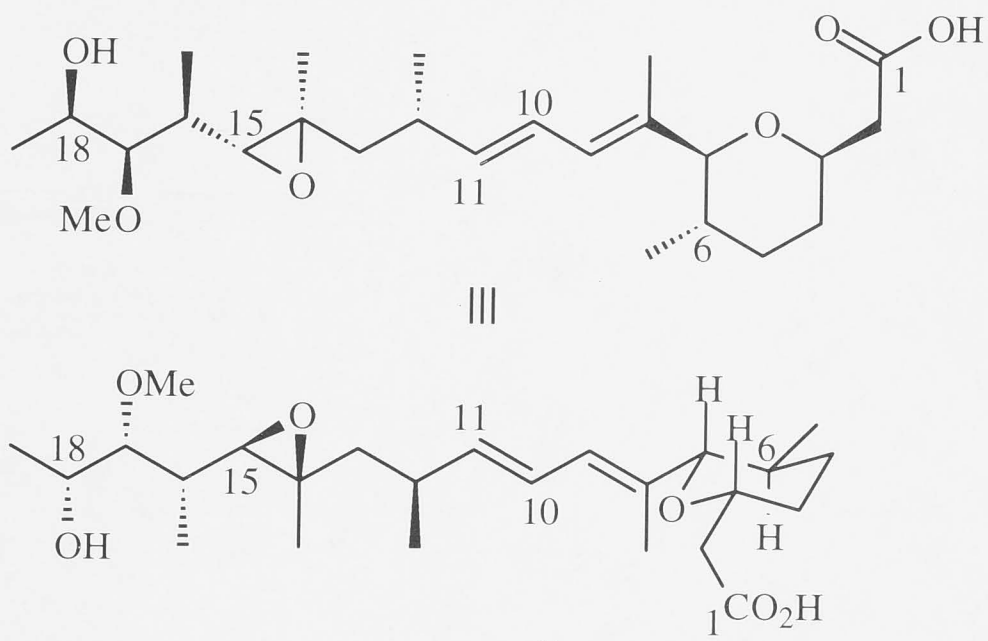
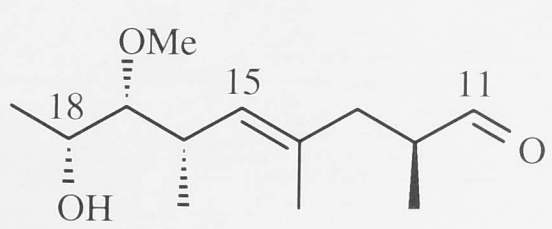
Different Representations of Herboxidiene and Certain Sub-structures

Different Representations of Herboxidiene and Certain Sub-structures

Throughout this thesis several different representations, as shown below, have been used to illustrate the structure of herboxidiene and various key sub-structures. These varying representations reflect the different ways in which such compounds have been portrayed in the literature.



Herboxidiene (**1**)



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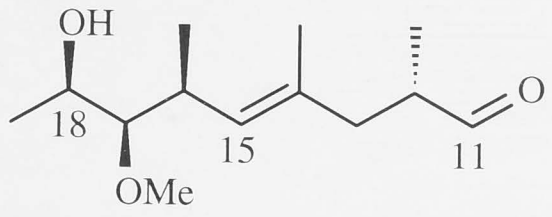
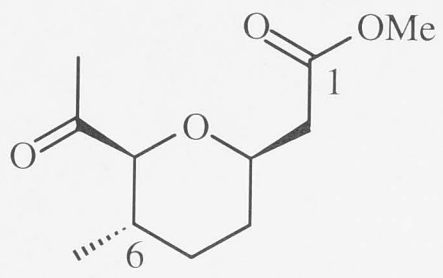


Herboxidiene Side Chain **94**



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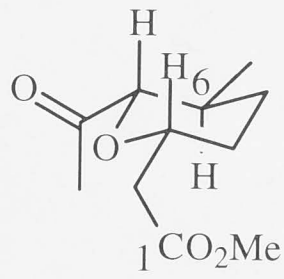
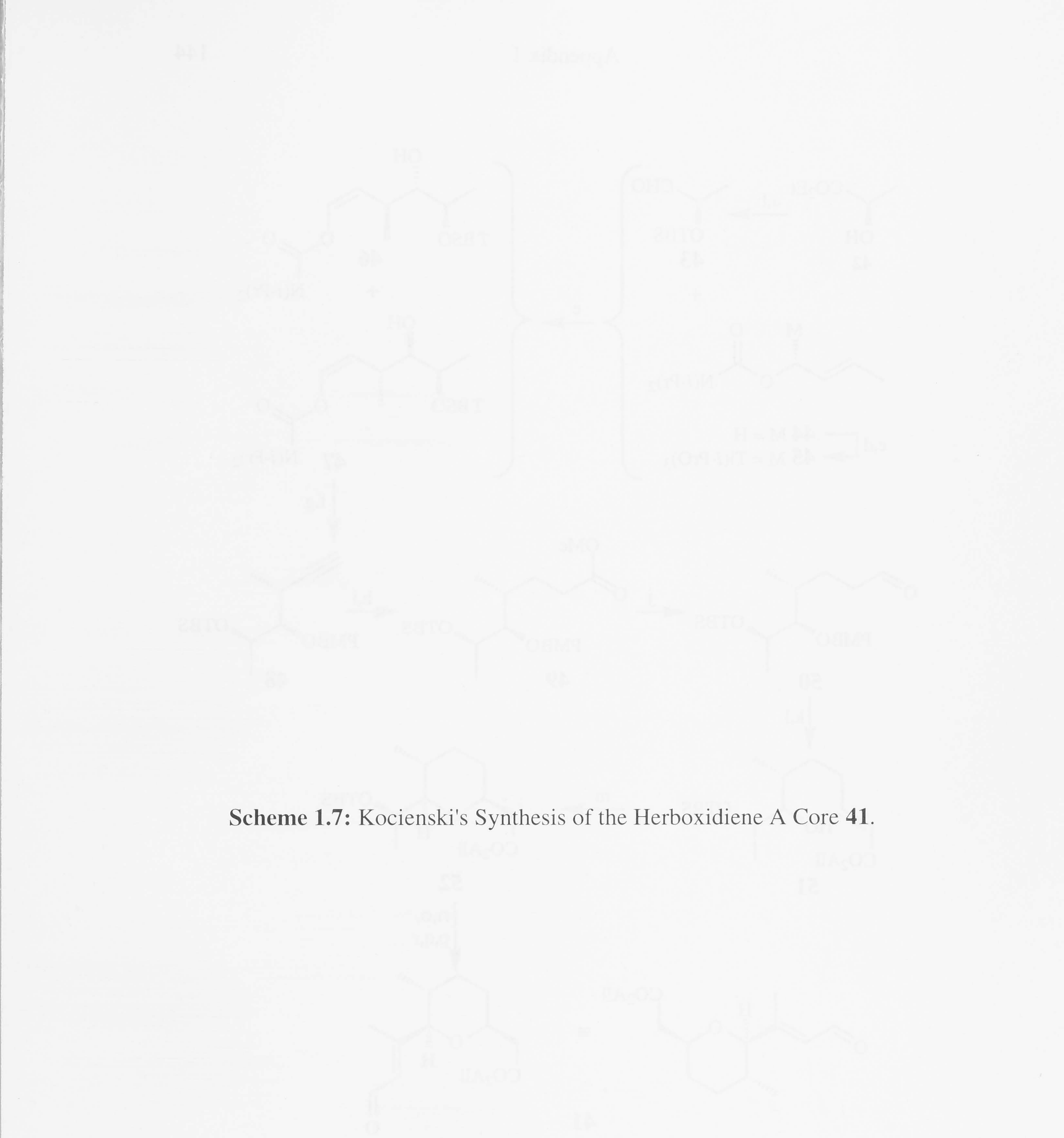


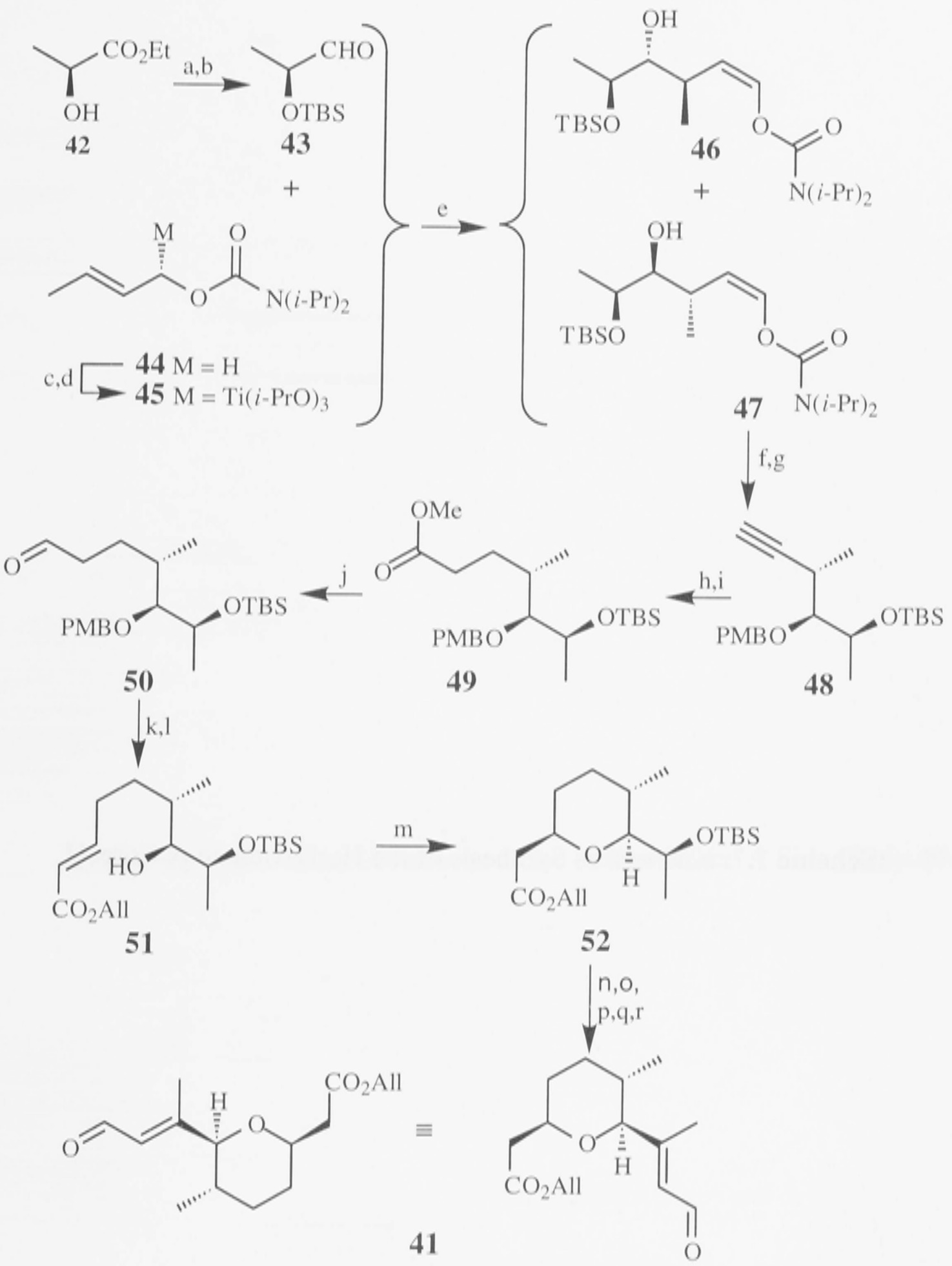
Herboxidiene Core **13**

APPENDICES

APPENDIX 1



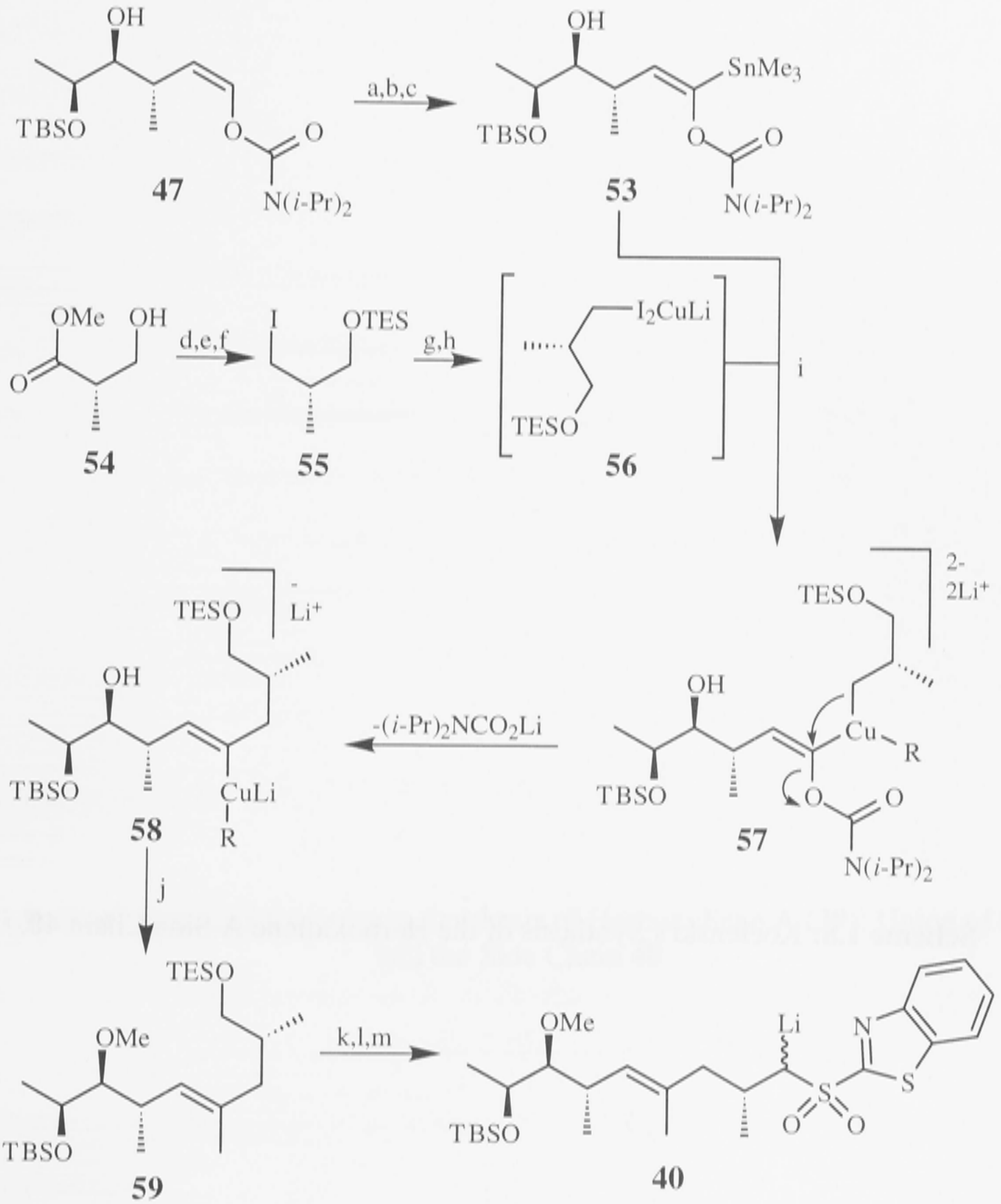
Scheme 1.7: Kocienski's Synthesis of the Herboxidiene A Core **41**.



Scheme 1.7: Kocienski's Synthesis of the Herboxidiene A Core **41**.

Reagents and conditions : (a) TBSCl, DMAP, imidazole/CH_2Cl_2, rt, 2 h; (b) DIBAL/toluene-CH_2Cl_2, -80 °C (c) BuLi, (-)-sparteine/cyclohexane-pentane, -80 °C, 3 h; (d) Ti(O-*i*-Pr)4/pentane, -80 °C, 20 min; (e) **43** and **45**, -80 °C (1.5 h) to rt (1 h); (f) PMBO-C(=NH)CCl_3, TMSOTf/Et_2O, rt; (g) *t*-BuLi/Et_2O, -20 °C; (h) BuLi/THF, -80 °C then $ClCO_2Me$; (i) H_2 (1 atm), Pd-C/EtOAc, rt; (j) DIBAL/CH_2Cl_2, -80 °C; (k) $(EtO)_2P(=O)CH_2CO_2All$, NaH/THF, -10 °C; (l) DDQ/CH_2Cl_2-H_2O, rt; (m) *t*-BuOK/THF, -65 °C; (n) TBAF, 4 Å molecular sieves/THF, rt; (o) PCC, 4 Å molecular sieves/CH_2Cl_2, rt; (p) $(EtO)_2P(=O)CH_2CO_2Bu^t$, NaH/THF, 0 °C to rt; (q) TFA, PhSMe/CH_2Cl_2; (r) $[Me_2N=CHCl]Cl$/THF-MeCN then $LiAlH(OBu^t)_3$.

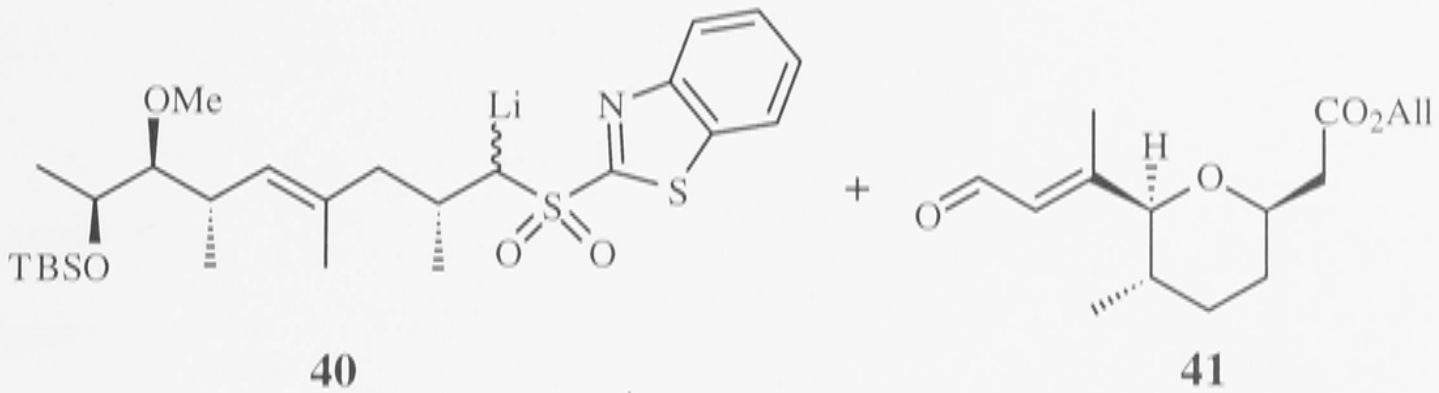
Scheme 1.8: Kocienski's Synthesis of the Herboxidiene A Side Chain **40**.



Scheme 1.8: Kocienski's Synthesis of the Herboxidiene A Side Chain **40**.

Reagents and conditions: (a) 4-Me-2,6-di-*t*-Bupyr, MeOTf/toluene, 70 °C; (b) *t*-BuLi/THF, -85 °C, rt; (c) Me_3SnCl, -85 °C, rt; (d) TESCl, DMAP, imidazole/CH_2Cl_2, rt; (e) DIBAL/toluene, -78 °C; (f) I_2, PPh_3, imidazole/CH_2Cl_2, rt; (g) *t*-BuLi/Et_2O-pentane, -80 °C; (h) CuBr.Me_2S, Me_2S-THF; (i) **53**, -35 to 0 °C; (j) MeI, HMPA/THF, -20 °C; (k) HF-pyridine/pyridine-THF, 0 °C to rt, 1 h; (l) 2-mercaptobenzothiazole, PPh_3, DEAD/THF, rt, 30 min; (m) $Mo(NH_4)_6$, H_2O_2/EtOH-H_2O, 0 °C to rt 5 h, rt, 24 h.

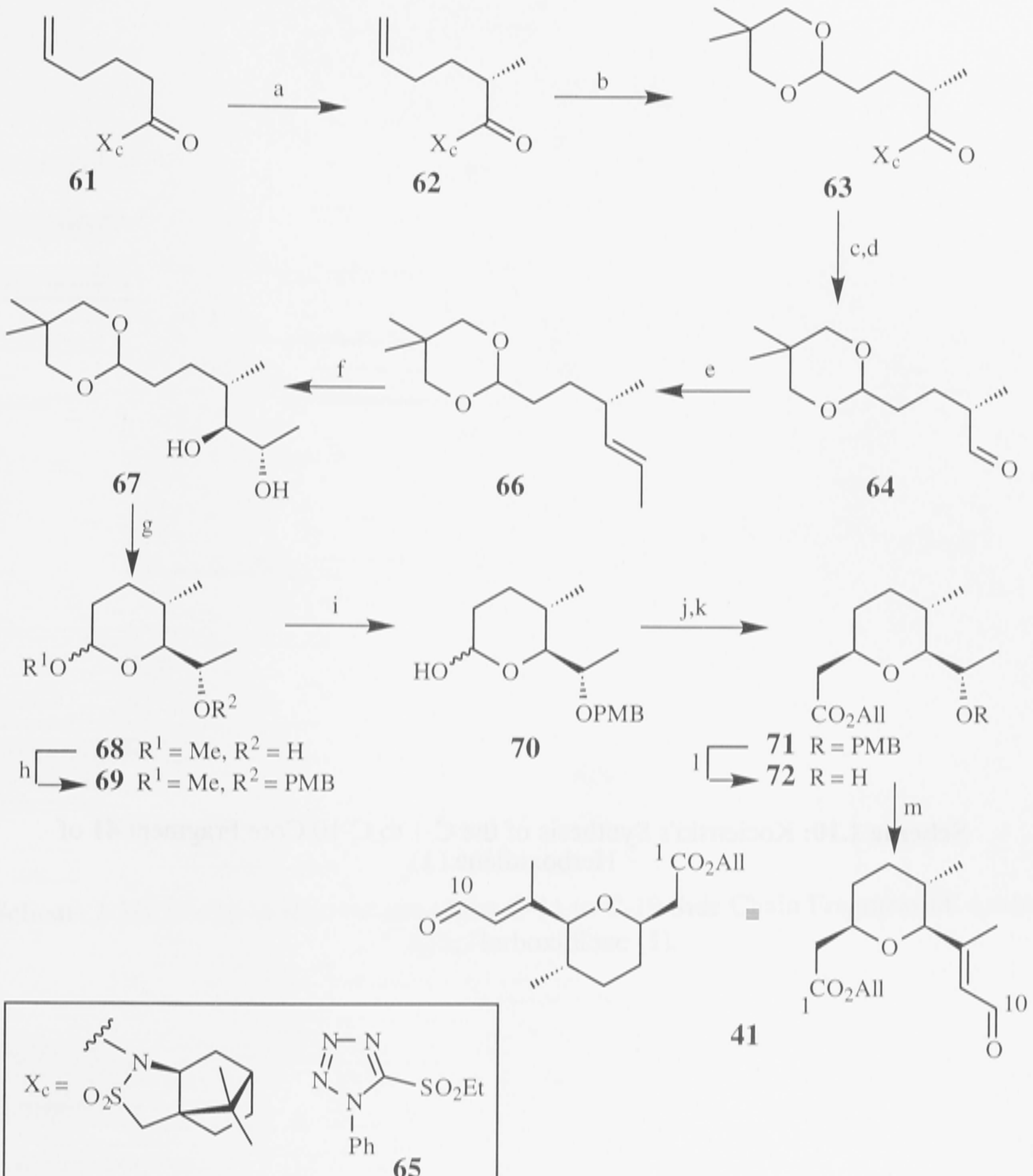
Scheme 1.9: Final Stages of Kocienski's Synthesis of Herboxidiene A (**39**): Union of the Core **41** and the Side Chain **40**.



Scheme 1.9: Final Stages of Kocienski's Synthesis of Herboxidiene A (**39**): Union of the Core **41** and the Side Chain **40**.

Reagents and conditions : (a) THF, -78 °C; (b) HF.pyr/THF-pyridine, rt; (c) $VO(acac)_2$, *t*-BuOOH/CH_2Cl_2, 0 °C; (d) $Pd(PPh_3)_4$, morpholine/THF, rt.

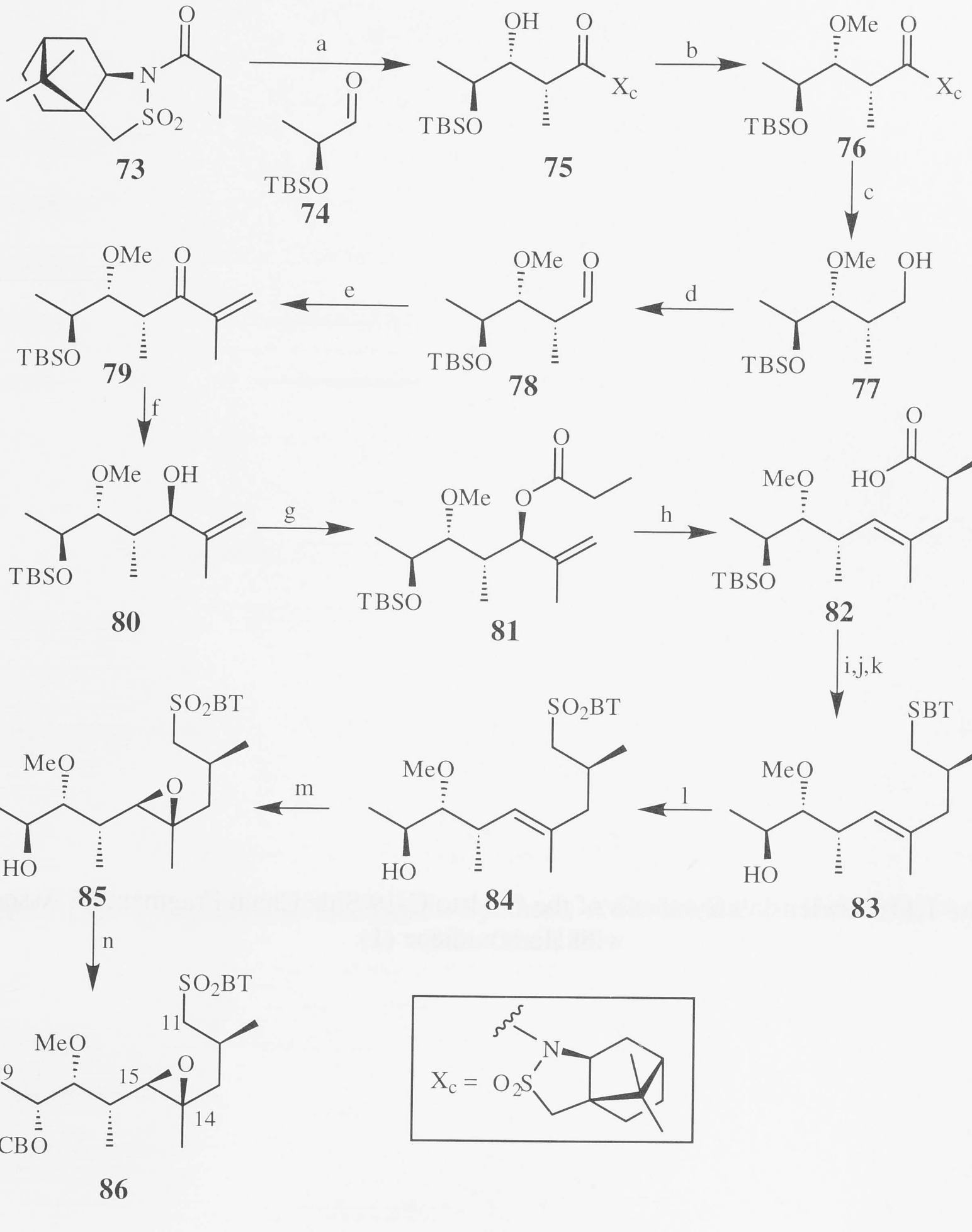
Scheme 1.10: Kocienski's Synthesis of the C-1 to C-10 Core Fragment **41** of Herboxidiene (**1**).



Scheme 1.10: Kocienski's Synthesis of the C-1 to C-10 Core Fragment **41** of Herboxidiene (**1**)

Reagents and conditions: (a) (i) BuLi, THF, -80 °C, 2 h; (ii) MeI, DMPU, -80 °C to rt, 12 h; (b) (i) O_3, MeOH-CH_2Cl_2 (1:3), -78 °C, 2 h; (ii) Me_2S, -78 °C to rt, 12 h; (iii) 2,2-dimethylpropane-1,3-diol, *p*-TsOH, PhMe, heat, (-H_2O), 12 h; (c) $LiAlH_4$, Et_2O, rt, 12 h; (d) Pyr.SO_3, Et_3N, DMSO, rt, 30 min; (e) sulfone **65**, KHMDS, DME, -60 °C, 45 min; (f) AD-mix α, $MeSO_2NH_2$, *t*-BuOH-H_2O (2:3), 0 °C, 18 h; (g) *p*-TsOH, MeOH, rt, 3d, α : β = 3 :1; (h) (i) KHMDS, THF, 0 °C, 20 min; (ii) PMBCl, TBAI, 0 °C to rt, 24 h; (i) AcOH-THF-H_2O (3 : 2 : 2), 65 °C, 2 h, α : β = 3 :2; (j) allyl diethyl phosphonoacetate, Cs_2CO_3, THF, heat, 18 h; (k) *t*-BuOK, THF, -65 °C, 10 min, pure *cis* isomer; (l) DDQ, 1:15 v/v H_2O/CH_2Cl_2, rt, 30 min; (m) 4 steps (see ref.10).

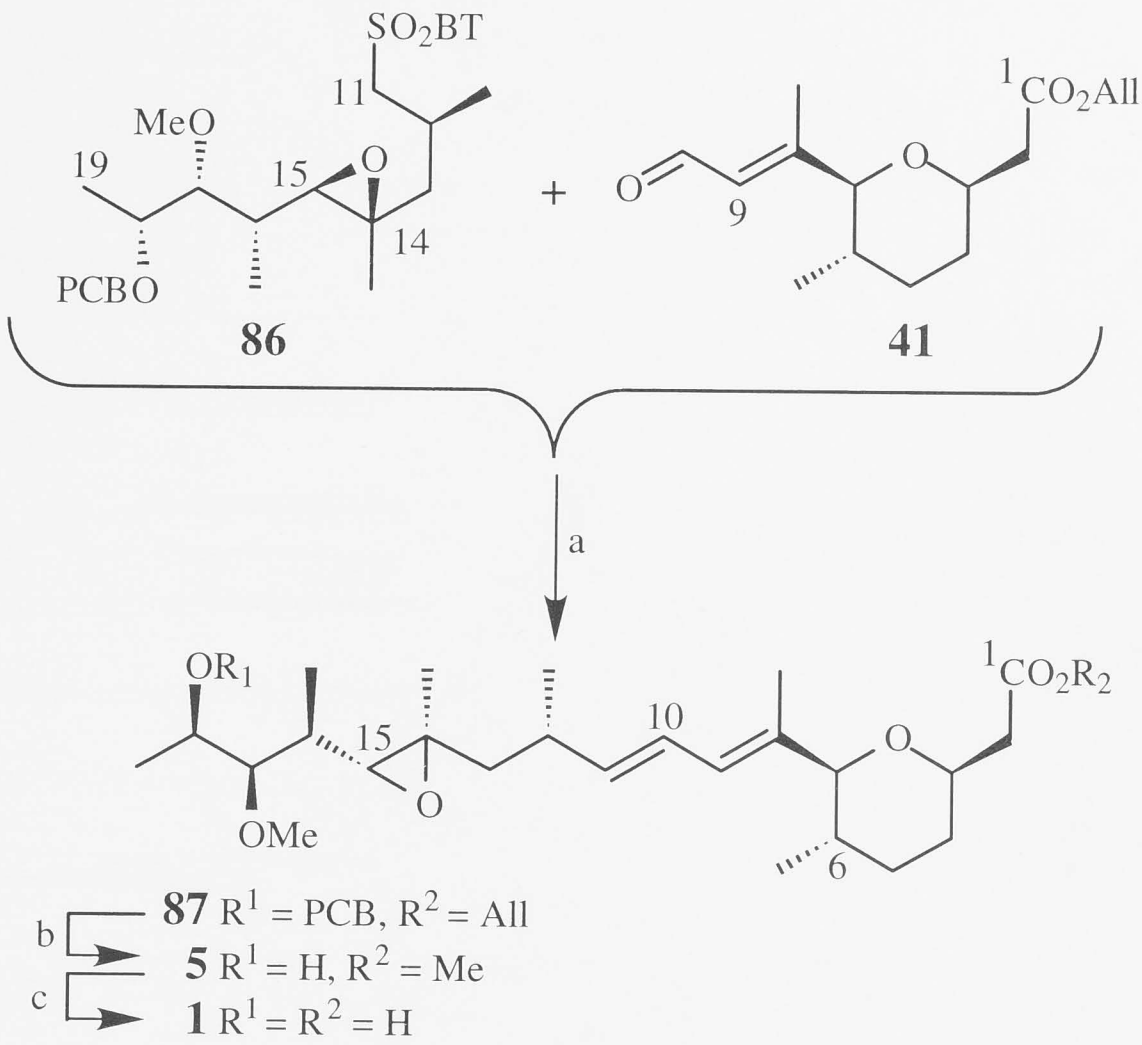
Scheme 1.11: Kocienski's Synthesis of the C-11 to C-19 Side Chain Fragment **86** Associated with Herboxidiene (**1**).



Scheme 1.11: Kocienski's Synthesis of the C-11 to C-19 Side Chain Fragment **86** Associated with Herboxidiene (**1**).

Reagents and conditions : (a) (i) Et_2BOTf, CH_2Cl_2, -5 °C; (ii) *i*-Pr_2NEt, 30 min; (iii) **74**, -78 °C, 3 h; (b) MeOTf, proton sponge, PhMe, 80 °C, 24 h; (c) $LiAlH_4$, Et_2O, 0 °C, 15 min; (d) Dess-Martin periodinane, CH_2Cl_2, 0 °C to rt, 2 h; (e) (i) CH_2=C(Me)MgBr, Et_2O, 0 °C, 1 h; (ii) DMP, CH_2Cl_2, rt, 4 h; (f) $LiAlH_4$, LiI, Et_2O, -100 °C, 1 h; (g) $(EtCO)_2O$, DMAP, pyridine, rt, 16 h; (h) (i) LDA, THF, -78 °C, 30 min; (ii) TBSCl, DMPU; (iii) -78 °C→Δ, 1 h; (iv) aq. HCl; (i) $LiAlH_4$, Et_2O, 0 °C, 10 min; (j) BTSH, Ph_3P, DIAD, THF, 0 °C to rt, 2 h; (k) TBAF.$3H_2O$, THF, rt, 32 h; (l) Mo(vi), H_2O_2, H_2O-EtOH, rt, 24 h; (m) $VO(acac)_2$, TBHP, CH_2Cl_2, -8 °C, 72 h; (n) (i) Ph_3P, DMAD, THF, 0 °C; (ii) PCBOH, 0 °C to rt, 3 h.

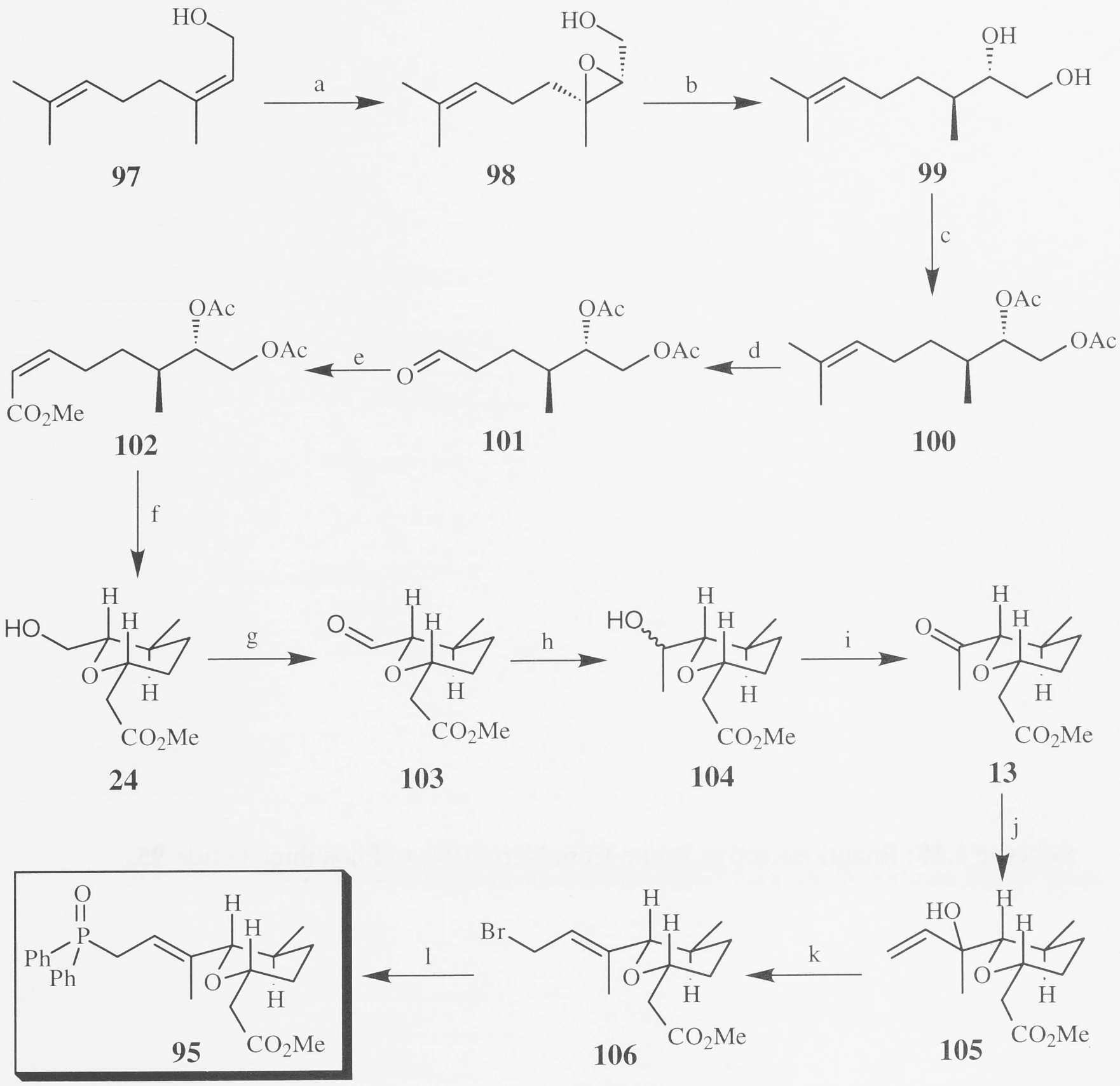
Scheme 1.12: Completion of Kocienski's Synthesis of Herboxidiene - Union of Core **41** and Side Chain **86**.



Scheme 1.12: Completion of Kocienski's Synthesis of Herboxidiene - Union of Core **41** and Side Chain **86**.

Reagents and conditions : (a) (i) LDA, THF, -78 °C, 15 min; (ii) **41**, -78 °C to -20 °C, 1.5 h; (b) K_2CO_3, MeOH, Δ, 2 h; (c) K_2CO_3, H_2O-MeOH (1 : 4), Δ, 1 h.

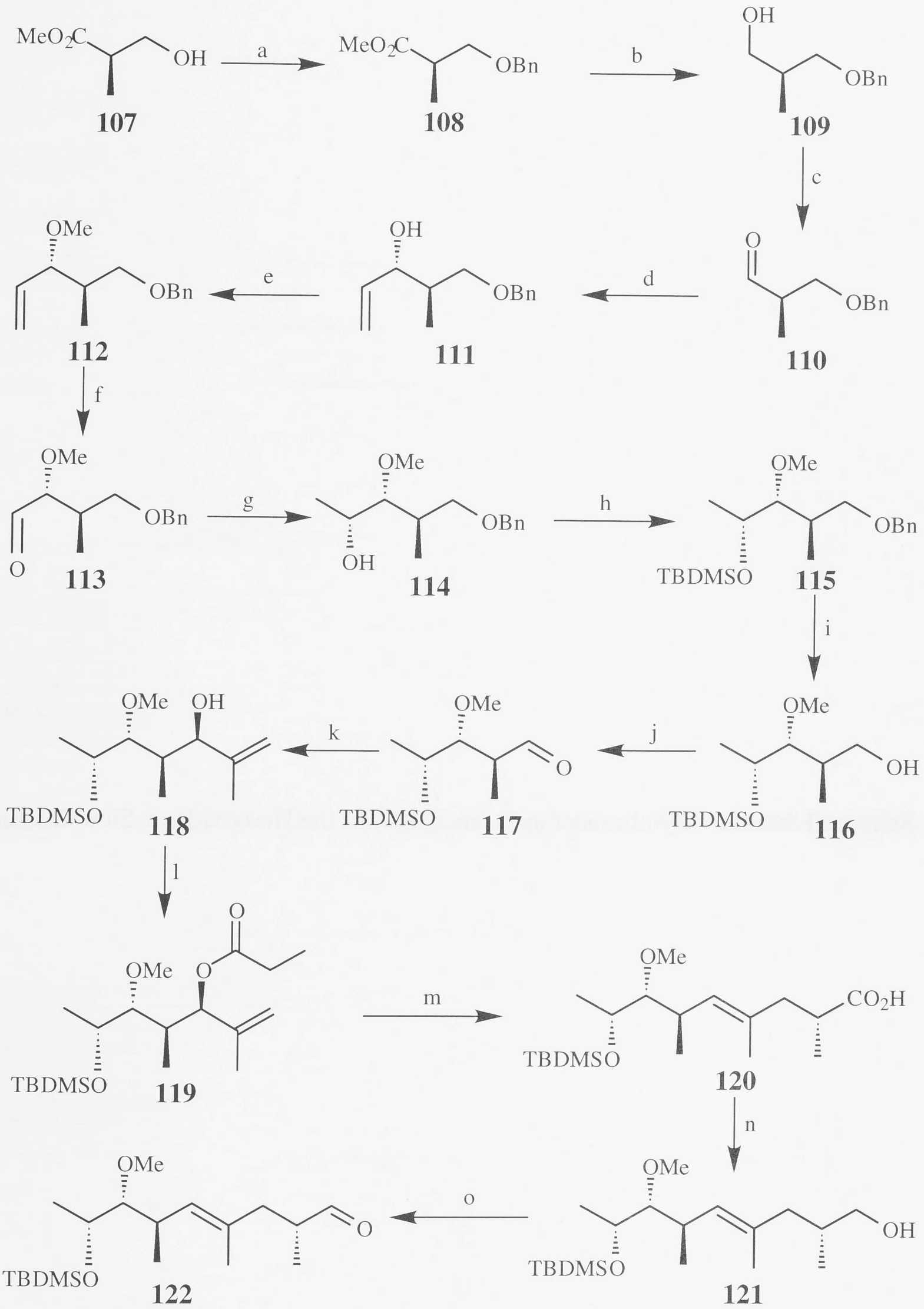
Scheme 1.15: Enantioselective Route from Nerol (**97**) to Phosphine Oxide **95**.



Scheme 1.15: Enantioselective Route from Nerol (**97**) to Phosphine Oxide **95**.

Reagents and conditions: (a) KSAE, diethyl *D*-(-)-tartrate/CH_2Cl_2; (b) $NaBH_3CN$, $BF_3.OEt_2$/THF; (c) Ac_2O, DMAP (trace)/pyridine, 18 °C; (d) O_3/CH_2Cl_2, -78 °C then PPh_3; (e) $MeO_2CCH_2P(O)(OCH_2CF_3)_2$, 18-crown-6/$CH_3CN$-complex, KHMDS/THF, -78 °C; (f) K_2CO_3/MeOH, rt, then MeOH, H_2SO_4 (trace), rt; (g) PCC, NaOAc/CH_2Cl_2, 18 °C; (h) MeMgCl/THF, 0 °C; (i) PCC, NaOAc/CH_2Cl_2, 18 ° C; (j) $H_2C=C(H)MgBr$/THF, -78 °C; (k) PBr_3/Et_2O, 0 °C; (l) Ph_2POEt/THF, reflux, 2 h.

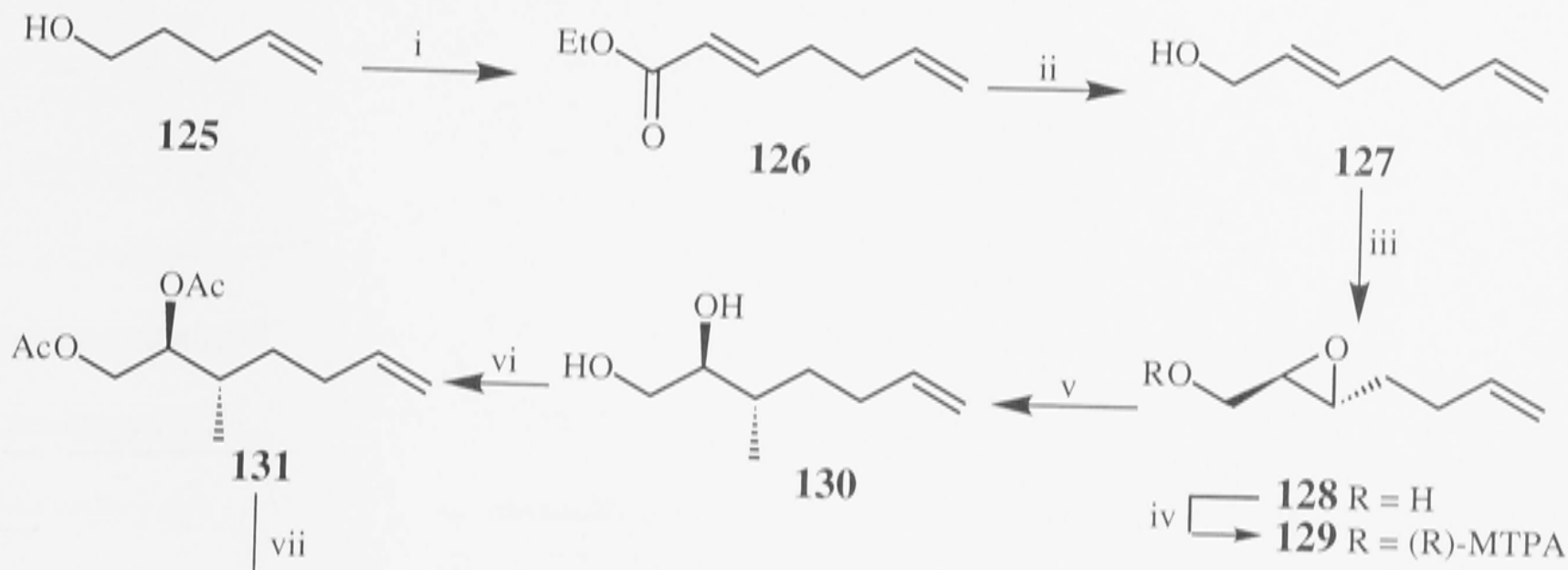
Scheme 1.16: Bui's Synthesis of an Isomer, **122**, of the Herboxidiene Side Chain.



Scheme 1.16: Bui's Synthesis of an Isomer, **122**, of the Herboxidiene Side Chain.

Reagents and conditions: (a) $BnOC(NH)CCl_3$, CF_3SO_3H (cat.)/CH_2Cl_2, 0 to 18 °C; (b) $LiAlH_4/Et_2O$, 0-5 °C; (c) Me_2SO, $Cl(CO)_2Cl/CH_2Cl_2$, -60 °C then NEt_3; (d) CH_2=C(H)MgBr/THF, 0 °C; (e) MeI, KH/THF, 0 to 18 °C; (f) O_3/CH_2Cl_2, -78 °C then Me_2S; (g) MeMgCl/THF, -78 °C; (h) TBDMSCl, imidazole/DMF, 60 °C; (i) H_2 (1 atm), 10% Pd on C/EtOH, rt; (j) Me_2SO, $Cl(CO)_2Cl/CH_2Cl_2$, -60 °C then NEt_3; (k) H_2C=C(Me)Br, *t*-BuLi, CuBr.DMS/Et_2O, -78 °C; (l) $(EtCO)_2O$, DMAP, pyridine, rt; (m) $KN(TMS)_2$/THF, then TMSCl-Et_3N, HMPA then heat at 45 °C; (n) $LiAlH_4/Et_2O$, 0 °C; (o) Me_2SO, $Cl(CO)_2Cl/CH_2Cl_2$, -60 °C then NEt_3.

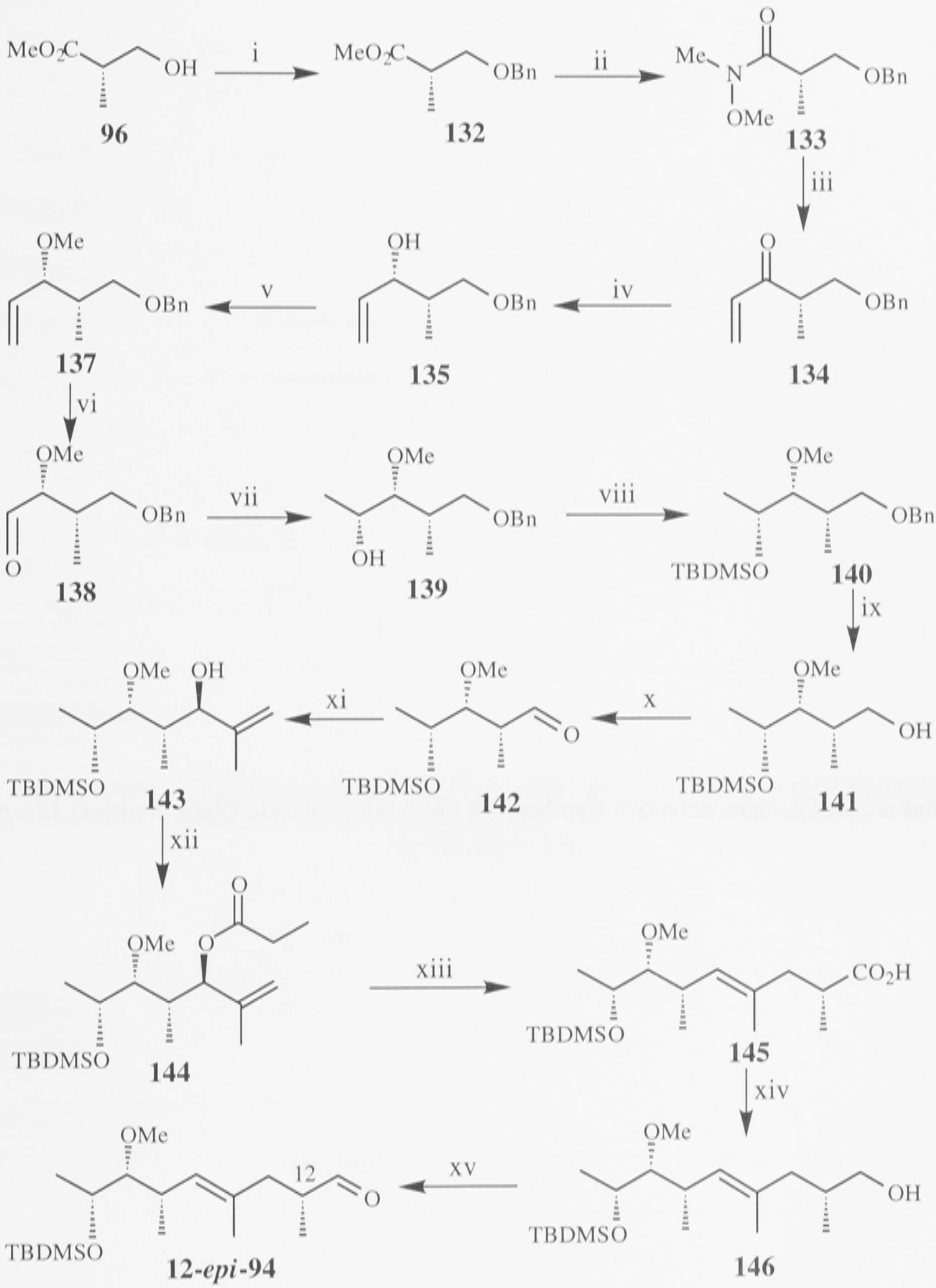
Scheme 2.1 and 2.2: Enantio- and Diastereo-selective Route to Herboxidiene Core Molecule **95**.



Scheme 2.1 and 2.2: Enantio- and Diastereo-selective Route to the Herboxidiene Core Molecule **95**.

Reagents and Conditions: (i) Swern oxidation then $Ph_3P{=}C(H)CO_2Et/CH_2Cl_2$, 2 h; (ii) DIBAL/ CH_2Cl_2, 2 h, -78 °C; (iii) KSAE, diethyl *D*(-)-tartrate/CH_2Cl_2; (iv) DMAP, NEt_3/CH_2Cl_2 then **119** and Mosher chloride; (v) Me_3Al/CH_2Cl_2, 0 °C to rt, 10 h; (vi) Ac_2O, DMAP(trace)/pyridine, 18 °C, 3 h; (vii) O_3/CH_2Cl_2 then PPh_3; (viii) $MeO_2CCH_2P(O)(OCH_2CF_3)_2$, 18-crown-6/$CH_3CN$-complex, $KN(TMS)_2$/THF, -78 °C; (ix) K_2CO_3/MeOH, rt, then MeOH, H_2SO_4 (trace), rt; (x) pyridine.SO_3 complex/DMSO, CH_2Cl_2, 0 °C; (xi) MeMgCl/THF, -78 °C to 0 °C; (xii) Dess-Martin periodinane/CH_2Cl_2, rt, 1 h; (xiii) $H_2C{=}C(H)MgBr$/THF, -78 °C; (xiv) PBr_3/Et_2O, 0 °C; (xv) Ph_2POEt/THF, reflux, 2 h.

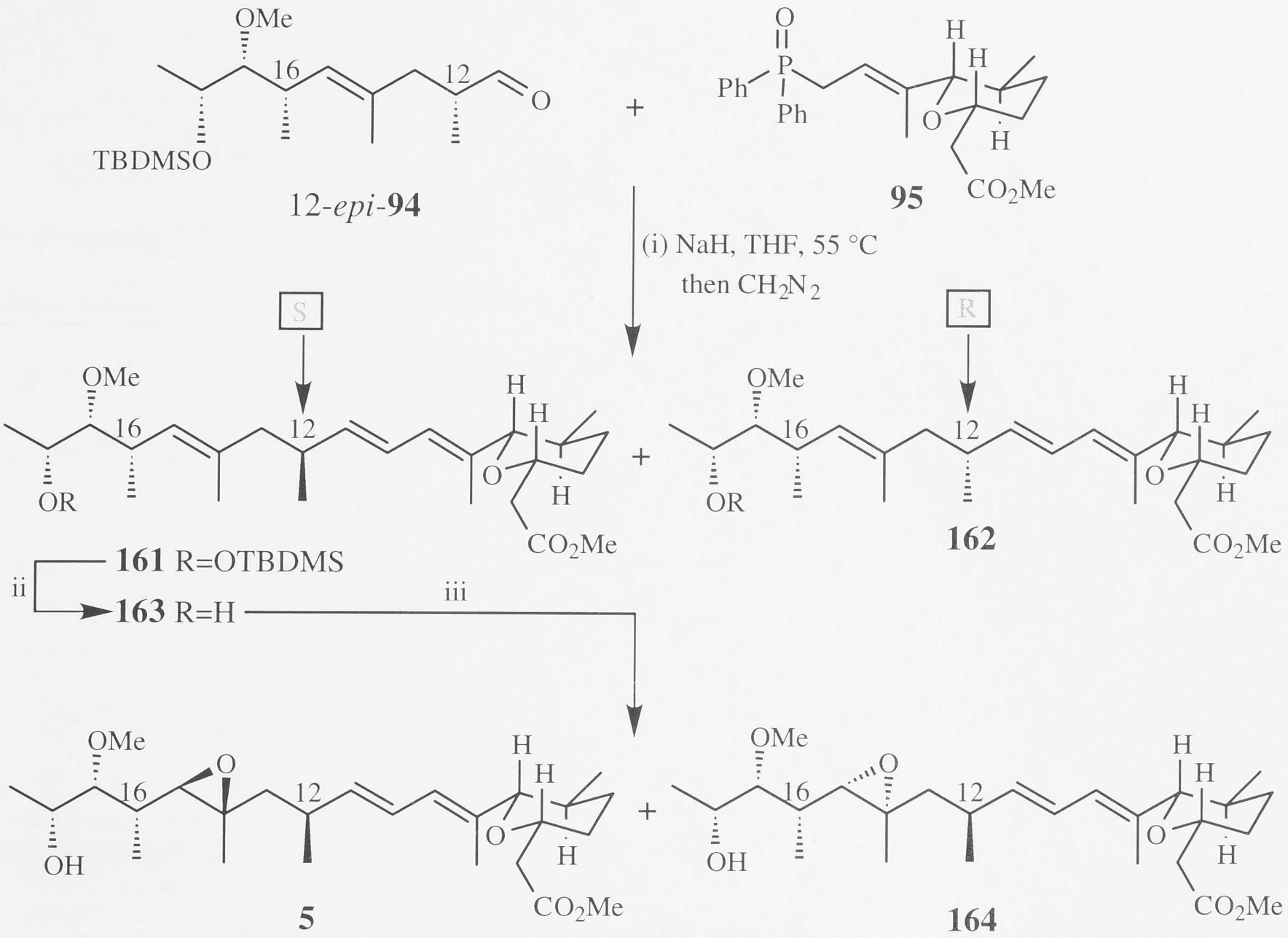
Scheme 3.1: Diastereoselective Synthesis of Herboxidiene Side Chain Synthon 12-*epi*-**94**.



Scheme 3.1: Diastereoselective Synthesis of Herboxidiene Side Chain Synthon 12-*epi*-**94**.

Reagents and conditions: (i) $BnOC(NH)CCl_3$, CF_3SO_3H (cat.)/CH_2Cl_2, 0 to 18 °C; (ii) Me(MeO)NH.HCl, *i*-PrMgCl/THF, -15 °C; (iii) $H_2C{=}C(H)MgBr$/THF, 0 °C; (iv) $Zn(BH_4)_2/CH_2Cl_2$, -78 °C; (v) MeI, KH/THF, 0 to 18 °C; (vi) O_3/CH_2Cl_2, -78 °C then Me_2S; (vii) Me_2Zn, $TiCl_4/CH_2Cl_2$, -78 °C; (viii) TBDMSCl, imidazole/DMF, 60 °C; (ix) H_2 (1 atm), $Pd(OH)_2$ on C/ THF, rt; (x) SO_3.pyridine complex/DMSO, CH_2Cl_2, rt; (xi) $H_2C{=}C(Me)Br$, *t*-BuLi, CuBr.DMS/Et_2O, -78 °C; (xii) $(EtCO)_2O$, DMAP, pyridine, rt; (xiii) LDA, HMPA/THF, TBDMSCl, -78 °C to 50 °C; (xiv) $LiAlH_4/Et_2O$, 0 °C; (xv) Dess-Martin periodinane/CH_2Cl_2, rt.

Scheme 4.1: Union of Core and Side Chain with Subsequent Regio-and Diastereo-controlled Epoxidation of the Resulting Triene **163**: Formation of Herboxidiene Methyl Ester (**5**).



Scheme 4.1: Union of Core and Side Chain with Subsequent Regio- and Diastereo-controlled Epoxidation of the Resulting Triene **163**: Formation of Herboxidiene Methyl Ester (**5**).

Reagents and Conditions : (i) NaH/THF, 55 °C then CH_2N_2; (ii) TBAF/THF, 0 °C to rt.; (iii) *t*-BuOOH, $VO(acac)_2/CH_2Cl_2$, -8 °C, 72 h.

APPENDIX 2

Pure Appl.Chem., in the press.

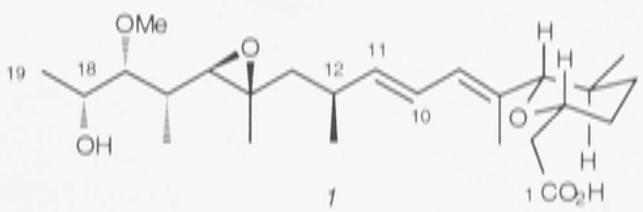
The Total Synthesis of Herboxidiene, a Complex Polyketide from *Streptomyces* Species A7847.

Martin Banwell,* [a] Malcolm McLeod,[a] Rajaratnam Premraj[a] and Gregory Simpson[b]

[a] *Research School of Chemistry, Institute of Advanced Studies, The Australian National University, Canberra, ACT 0200, Australia.* [b] *CSIRO Molecular Science, Bag 10, Clayton South, Victoria 3169, Australia.*

Abstract: A formal total synthesis of the polyketide herboxidiene (*1*) has been achieved by Horner-Wittig coupling of the side-chain fragment 12-*epi*-(*2*) with the tetrahydropyran-2-acetic acid derivative (*3*) followed by desilylation of the resulting triene (*19*) and hydroxyl-directed mono-epoxidation of the ensuing *bis*-homoallylic alcohol (*20*).

In 1992 a group at Monsanto (USA) detailed (ref. 1) the near complete structural elucidation of the polyketide herboxidiene (*1*, a.k.a. TAN-1609) which they had isolated from *Streptomyces chromofuscus* A7847. The same group also revealed (ref. 1) that the molecule displays potent and highly selective phytotoxic properties such that at application rates of 35 g/acre it selectively controls various crop pests such as oilseed rape, wild buckwheat and morning glory while being harmless to wheat. Such properties, which are remarkable for a polyketide, prompted efforts by Edmund's group at Novartis AG (ref. 2) to re-isolate herboxidiene and then, through a combination of X-ray crystallographic, chemical degradation and chemical synthesis studies, to establish the full stereochemistry associated with compound (*1*). Such studies were accompanied by extensive SAR-work (ref. 3) as well as, thus far, unsuccessful efforts (ref. 2,3) to develop a total synthesis of the compound. At about the same time three Japanese groups (ref. 4-6) reported isolating herboxidiene from various fermentation processes. One of these groups (ref. 4) reported that the compound up-regulates gene expression of low density lipoprotein receptors (and thereby lowering cholesterol levels in blood plasma) while another has reported (ref. 6) that it blocks the cell-cycle at the G2 phase in human and murine tumour cells by inducing apoptosis.



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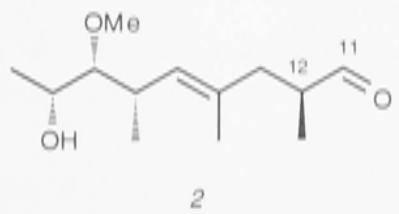

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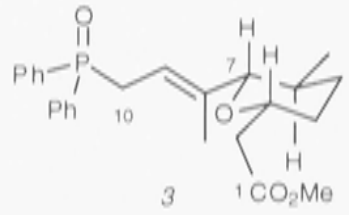

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The first total synthesis of herboxidiene was reported recently by Kocienski and co-workers (ref. 7) who adapted elegant earlier work (ref. 8) that had culminated in the preparation of herboxidiene A, a diastereoisomer of the natural product. We now report a (formal) total synthesis of the title compound that differs, in a number of respects, from that described by the Glasgow group (ref. 7). The present work exploits the Katsuki-Sharpless epoxidation reaction, a chiral-pool starting material and substrate-directed

transformations for establishing the correct stereochemistry associated with eight of the nine centres of chirality contained in the target molecule (*1*).

As enunciated previously, (ref. 9,10) an obvious disconnection of target (*1*) is between C10 and C11 so as to create substructures such as the side-chain molecule (*2*) and phosphine oxide core (*3*) that could be coupled to one another through a Horner-Wittig (HW) reaction. It was anticipated that the epoxide moiety associated with herboxidiene could be introduced *via* C18-hydroxyl-directed epoxidation after the HW-coupling step (ref. 7,11). We have recently detailed (ref. 9) a synthesis of compound (*3*), that starts with the Katsuki-Sharpless asymmetric epoxidation of nerol, and shown that this phosphine oxide does couple in the appropriate fashion (ie with high *E*-selectivity) with model aldehydes. A highly diastereoselective synthesis of the herboxidiene side-chain is shown in Fig. 1 and starts with the commercially available methyl (2*S*)-3-hydroxy-2-methylpropionate (*4*) (ALDRICH, 99% ee). Compound (*4*) was *O*-benzylated under conditions which avoid racemisation (ref. 12) and the resulting ether (*5*) (ref.13) (97%) converted into the corresponding Weinreb amide (*6*) (98%) $\{[\alpha]_D = +4.6$ (c = 2.0)$\}$ using *i*-propylmagnesium chloride as base. Treatment of the latter compound with vinylmagnesium bromide afforded, after acidic workup, the expected conjugated ketone (*7*) (92%) which underwent a chelation controlled 1,2-reduction with zinc borohydride (ref. 14) at -78¡C to give a *ca.* 8:1 mixture of allylic alcohol (*8*) (ref. 15) (83%) $\{[\alpha]_D = -9.6$ (c = 2.8)$\}$ and the corresponding *anti*-isomer (*ca.* 10%) $\{[\alpha]_D = +28.2$ (c = 2.5)$\}$ which could be readily separated from one another by preparative HPLC. *O*-Methylation of compound (*8*), to give (*9*) (85%) $\{[\alpha]_D = +12.2$ (c = 1.3)$\}$, followed by ozonolytic cleavage of the carbon-carbon double bond afforded the unstable aldehyde (*10*) (90%) $\{[\alpha]_D = +22.5$ (c = 2.2)$\}$ which was immediately reacted with dimethylzinc in the presence of $TiCl_4$ (ref. 16) to give alcohol (*11*) (70%) $\{[\alpha]_D = +8.6$ (c = 2.8)$\}$ as the only isolable reaction product. The readily derived TBDMS-ether (*12*) (80%) $\{[\alpha]_D = +10.4$ (c = 2.5)$\}$ was subjected to hydrogenolytic debenzylation and the ensuing 1¡-alcohol (*13*) (80%) oxidised to the aldehyde (*14*) using the Parikh-Doering reagent (ref. 17). Reaction of the last compound with the Gilman reagent obtained from 2-bromopropene then gave, *via* a chelation controlled process, the allylic alcohol (*15*) [70% from (*13*)] $\{[\alpha]_D = +3.2$ (c = 1.2)$\}$. The derived propionate ester (*16*) (90%) $\{[\alpha]_D = -22.0$ (c = 1.6)$\}$ was subjected to an Ireland-Claisen rearrangement (ref. 10,18) involving sequential treatment with LDA then TBDMSCl in HMPA/THF from -78 to 50 ¡C. The (12*R*)-stereochemistry and the (*E*)-geometry about the double-bond in the ensuing γ,δ-unsaturated carboxylic acid (*17*) (75%) $\{[\alpha]_D = +5.8$ (c = 2.2)$\}$ were initially proposed on the basis of the well-defined outcomes associated with the Ireland-Claisen rearrangements of related substrates under the same reaction conditions (ref. 7,10). $LiAlH_4$-promoted reduction of compound (*17*) afforded the corresponding alcohol (*18*) (80%) $\{[\alpha]_D = +6.4$ (c = 1.6)$\}$ which was converted, using the Dess-Martin periodinane, into the unstable C12-epimer (80%) of the target aldehyde (*2*), *viz.* 12-*epi*-(*2*).

The stage was now set for the crucial HW-reaction involving phosphine oxide (*3*) (ref. 9) and, thence, the final stages of the total synthesis. In the event coupling of aldehyde 12-*epi*-(*2*) and phosphine oxide (*3*) could be effected with sodium hydride. The reaction was accompanied by epimerisation of the former compound with the result that a 3:2 mixture of triene (*19*) (39%) $\{[\alpha]_D = +0.4$ (c = 2.3)$\}$ and its C12-epimer (26%) $\{[\alpha]_D = +18.4$ (c = 1.5)$\}$ was obtained. These products could be separated from one another using semi-preparative HPLC techniques and desilylation of the chromatographically less-mobile compound (*19*) was accomplished using tetra-*n*-butylammonium fluoride (TBAF) in THF.

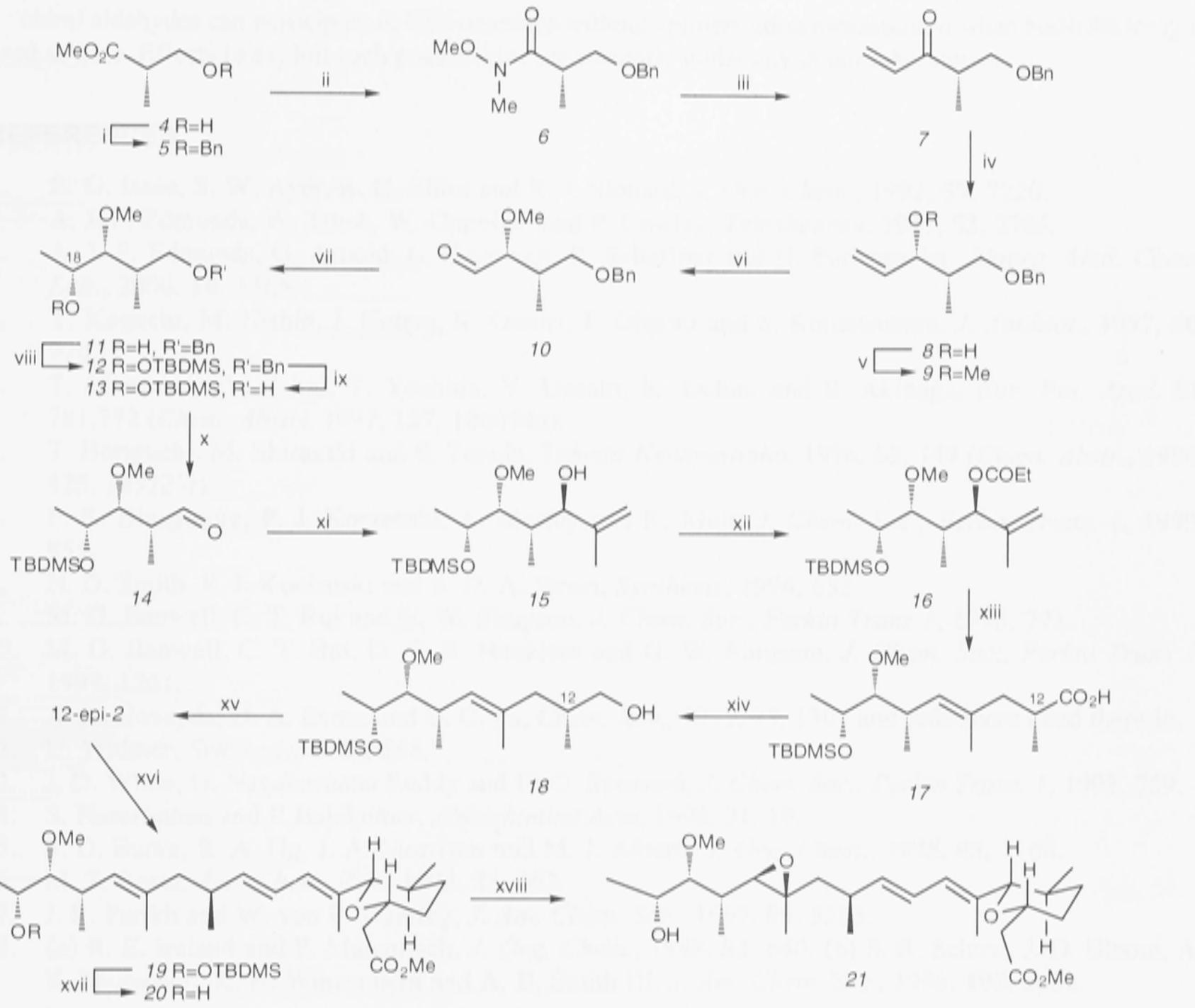

Fig. 1 *Reagents and conditions*: (i) $BnOC(NH)CCl_3$ (1.2 mole equiv.), CH_2Cl_2, CF_3SO_3H (cat.), *ca.* 0 to18 ¡C, 16 h; (ii) Me(MeO)NH.HCl (1.55 mole equiv.), *i*-PrMgCl (3.0 mole equiv.), THF, -15 ¡C, 0.5 h; (iii) $H_2C{=}C(H)MgBr$ (1.5 mole equiv.), THF, 0 ¡C, 0.5 h; (iv) $Zn(BH_4)_2$, CH_2Cl_2, -78 to 0 ¡C, 4.5 h; (v) MeI (2.5 mole equiv.), KH (2.5 mole equiv.), THF, 0-18 ¡C, 6 h; (vi) O_3 (excess), CH_2Cl_2, -78 ¡C, 1 h then DMS (1.0 mole equiv.), -30-18 ¡C, 0.5 h; (vii) Me_2Zn (1.0 mole equiv.), $TiCl_4$ (1.0 mole equiv.), THF, -78 ¡C, 0.5 h; (viii) TBDMSCl (2.0 mole equiv.), imidazole (3.0 mole equiv.), DMF, 60 ¡C, 3 h; (ix) H_2 (1 atm.), $Pd(OH)_2$, THF, 18 ¡C, 1 h; (x) SO_3/pyridine (3.0 mole equiv.), DMSO, CH_2Cl_2, 0 to 18 ¡C, 4 h then Et_3N, 0 ¡C, 1.0 h; (xi) $H_2C{=}C(Me)Br$ (13.5 mole equiv.), *t*-BuLi (27 mole equiv.), CuBr.DMS (6.9 mole equiv.), Et_2O, -78 ¡C, 3 h; (xii) $(EtCO)_2O$ (2.5 mole equiv.), DMAP (cat.), C_6H_5N, 18 ¡C, 16 h; (xiii) LDA (1.3 mole equiv.), HMPA/THF (1:2 v/v), -78 ¡C, 0.5 h then TBDMSCl (1.3 mole equiv) then heat at 50 ¡C, 6 h; (xiv) $LiAlH_4$ (1.0 mole equiv.), THF, 0 to 18 ¡C, 6 h; (xv) Dess-Martin periodinane (2.5 mole equiv.), CH_2Cl_2, 0 to 18 ¡C, 4 h; (xvi) Compound *3* (1.0 mole equiv.) NaH (10 mole equiv.), THF, 55 ¡C, 2 h then CH_2N_2 (excess), CH_2Cl_2, 18 ¡C, 16 h; (xvii) TBAF (1.5 mole equiv.), THF, 0-18 ¡C, 6 h; (xviii) *t*-BuOOH (3.0 mole equiv.), $VO(acac)_2$ (1.0 mole %), CH_2Cl_2, -8 ¡C, 72 h.

The resulting alcohol (*20*) (68%) was then reacted with *tert*-butylhydroperoxide in the presence of $VO(acac)_2$ and in this way a *ca.* 4:1 mixture of herboxidiene methyl ester (*21*) (73%) {$[\alpha]_D$ = + 1.3 (c = 0.2), lit. (ref. 7) $[\alpha]_D$ = + 0.9 (c = 0.7)} and an isomer was obtained. These epoxides could also be separated from one another by semi-preparative HPLC and the spectral data obtained on the former product matched, in all respects, those reported by Kocienski and co-workers (ref. 7).

The acquisition of herboxidiene methyl ester constitutes a formal total synthesis of herboxidiene because it has been shown that the former material can be converted into compound (*1*) by conventional hydrolysis (ref. 7). In principle the problems of controlling C-12 stereochemistry could be addressed by effecting Ireland-Claisen rearrangement of the (*E*)-silylketene acetal derived from propionate ester (*16*) so as to give 12-*epi-(17)* and, thence, aldehyde (*2*) (ref. 7,18b). Furthermore, there are indications in the literature (ref. 18b) that α-

chiral aldehydes can participate in HW-reactions without epimerisation/racemisation when $NaN(SiMe_3)_2$ is used as base. Efforts to exploit such possibilities are currently underway in our laboratories.

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Improved Synthetic Route to Enantiomerically Pure Samples of the Tetrahydropyranylacetic Acid Core Associated with the Phytotoxic Polyketide Herboxidiene.

Martin G. Banwell,[A,B] Malcolm D. McLeod, [A,C] Rajaratnam Premraj [A] and Gregory W. Simpson[D]

A Research School of Chemistry, Institute of Advanced Studies, The Australian National University, Canberra, ACT 0200

B To whom correspondence should be addressed

C School of Chemistry, F11, University of Sydney, Camperdown, NSW 2006

D CSIRO Molecular Science, Private Bag 10, Rosebank MDC, Clayton South, Victoria 3169

Abstract

The phosphine oxide (2), which embodies the tetrahydropyranylacetic acid core associated with the phytotoxic polyketide herboxidiene (1) and which is a key intermediate in a projected synthesis of this natural product, has now been prepared in a highly enantio- and diastereo-selective manner. The pivotal steps in this new and improved synthesis of compound (2) involve Sharpless asymmetric epoxidation of the allylic alcohol (4) to give epoxide (7) and subsequent ring-cleavage of the latter compound with trimethylaluminium to give diol (9). The derived acetate (10) is then readily ozonolysed to give the previously reported aldehyde (11), although now in high enantiomeric excess. Compound (11) can be elaborated, by established chemistry, to the target oxide (2).

Introduction

In 1992 a group at Monsanto (USA) detailed[1] the near complete structural elucidation of the polyketide herboxidiene (1, a.k.a. TAN-1609) which they had isolated from *Streptomyces chromofuscus* A7847. The same group also revealed[1] that the molecule displays potent and highly selective phytotoxic properties such that at application rates of 35 g/acre it selectively controls various crop pests such as oilseed rape, wild buckwheat and morning glory while being harmless to wheat. Such properties, which are remarkable for a polyketide, prompted efforts by Edmund's group at Novartis AG[2] to re-isolate herboxidiene and then, through a combination of X-ray crystallographic, chemical degradation and chemical synthesis studies, to establish the full stereochemistry associated with compound (1). Several Japanese groups[3-5] have also isolated herboxidiene and one has determined[5] that the compound up-regulates the gene expression of the low-density lipoprotein receptor while another has reported[3b] that it inhibits the growth of various murine and human tumour cell lines. The interesting biological profile of this natural product has prompted various attempts to effect its preparation by total synthesis.[2,6-9] In connection with our own efforts in this area[8,9] we have reported[9] a twelve step route to phosphine oxide (2) which embodies the tetrahydropyranylacetic acid core associated with compound (1). However, a deficiency associated with our synthesis of (2) is the need to carry out, at the initial stage, a Sharpless asymmetric epoxidation (SAE) of nerol (3) which delivers the corresponding epoxy-alcohol in only *ca.* 50% enantiomeric excess (ee).[9] Since, with the exception of target (2), all the compounds in the reaction sequence, including the initially formed epoxy-alcohol, are oils the only opportunity to obtain enantiopure phosphine oxide (2) was by repeated recrystallisation of this compound. However, the attendant loss of material was significant thus prompting us to examine alternate routes to this compound. As a consequence, we now describe a new synthesis of phosphine oxide (2) that circumvents the above-mentioned problems.

Results and Discussion

In contrast to the situation with (*Z*)-1,2,2-trisubstituted alkenes (e.g. nerol), the SAE of allylic alcohols proceeds in high enantiomeric excess (ee) when (*E*)-1,2-disubstituted alkenes are employed as substrates.[10] Consequently, the allylic alcohol (4) was chosen as the substrate for SAE on the basis that the product epoxide would be obtained in high ee. In addition, it was anticipated that nucleophilic methylation of the product epoxide could be achieved in a regio- and diastereo-selective manner so as to install the methyl group required at C6 in the target molecule (2). The pivotal alkene (4) was readily prepared (Scheme 1) by a one-pot procedure involving initial oxidation of commercially available (ALDRICH) alcohol (5) to the corresponding aldehyde. Using a modification of procedures reported by Barrett,[11] Lee[12] and Taylor,[13] this latter compound was subjected to *in situ* Wittig olefination with (carbethoxymethylene)-triphenylphosphorane. In this manner the α,β-unsaturated ester (6) (98%) was obtained and the illustrated (*E*)-configuration about the Δ^2-double-bond was established by ^{1}H n.m.r. analysis ($J_{H2,H3}$ = 15.6 Hz). DIBALH-promoted 1,2-reduction of compound (6) proceeded smoothly to give the target alcohol (4) in 85% yield and the various spectral data derived from this material were in full accord with the assigned structure. SAE of compound (4) was effected under standard conditions using catalytic quantities of diethyl *D*-(-)-tartrate and in this manner the anticipated epoxy-alcohol (7) (70%) was obtained. This latter material was converted, under standard conditions, into the corresponding Mosher ester (8) (42%) which was obtained as a single diastereoisomer (as determined by ^{1}H n.m.r. analysis) and thus suggesting that the precursor alcohol was of >95% ee. This interpretation was confirmed by, *inter alia*, converting the racemic modification of epoxide (7) [prepared by treating alkene (4) with *m*-chloroperbenzoic acid] into the corresponding 1:1 mixture of compound (8) and its diastereoisomer and observing that these Mosher esters were readily differentiated from one another by 300 MHz ^{1}H n.m.r. spectroscopy (see Experimental Section).

Treatment of epoxy-alcohol (7) with three molar equivalents of trimethylaluminium[14] in CH_2Cl_2 at 18 °C for 10 h resulted in its smooth conversion into diol (9) (83%) the

structure of which follows from its transformation into the previously reported[9] aldehyde (11). Thus, two-fold acetylation of compound (9) was achieved under standard conditions and the resulting diacetate (10) (96%) was subjected to ozonolytic cleavage followed by reductive work-up with triphenylphosphine to give the aldehyde (11) (79%). This last compound proved identical (as judged by ^{1}H n.m.r., ^{13}C n.m.r. , i.r. and mass spectral analysis) with the samples of the aldehyde obtained by our previous route.[9] As expected, however, the specific rotation of the material generated by the present route was effectively double $\{[\alpha]_D = +7.3$ *vs* $[\alpha]_D = +3.8\}$ that observed for the sample of aldehyde (11) obtained earlier.

The completion of the synthesis of the target phosphine oxide (2) followed the route established earlier although various minor modifications to the previously reported methods[9] are detailed here-in. Thus, subjection of compound (11) to Still-Gennari modification[15] of the Wadsworth-Emmons reaction afforded the alkene (12) (80%) as the only isolable product of reaction. The (*Z*)-configuration about the double-bond in this product follows from the magnitude of the vicinal spin-spin coupling (J = 11.5 Hz) observed between H-2 and H-3 in the ^{1}H n.m.r. spectrum of this material. Treatment of compound (12) with potassium carbonate in methanol resulted in removal of the acetate groups and a subsequent intramolecular Michael addition reaction to give the tetrahydropyranylacetic acid ester (13) which was accompanied by varying quantities of the corresponding acid. Consequently, the crude reaction mixture was treated with acidic methanol and in this manner compound (13) was obtained in 71% yield. Oxidation of hydroxy-ester (13) under Parikh-Doering conditions (pyridine-SO_3 activated DMSO)[16] afforded the corresponding aldehyde (14) (60%) which proved spectroscopically identical with the sample we had obtained by our previous route. In addition, the optical rotation of this material effectively matched that reported[2] by Edmunds for enantiomerically pure material. The conversion of aldehyde (14) into methyl ketone (15) proved especially troublesome and, thus far, we have not been able satisfactorily resolve these difficulties. After considerable experimentation with a range of nucleophilic methylating agents, methyl magnesium chloride proved to be most effective in adding to the aldehyde moiety associated

with compound (14). The resulting mixture of diastereoisomeric 2°-alcohols was immediately oxidised with the Dess-Martin periodinane[17] and the corresponding methyl ketone (15) thereby obtained albeit in only 17% yield. Nevertheless, the optical rotation of this compound matched that reported for a sample obtained by ozonolytic cleavage of herboxidiene itself.[2]

Elaboration of ketone (15) to the target phosphine oxide (2) followed previously established procedures[9] and involved initial reaction of the former compound with vinyl magnesium bromide. This resulted in generation of the desired 3°-alcohol (60%) which was treated with phosphorous tribromide to afford the allylic bromide (16) (93%). The latter compound engaged in a Michaelis-Arbuzov reaction with diphenylethoxyphosphine to deliver the target compound (2) (85%) as a crystalline solid after flash chromatography. The melting point of this compound (m.p. = 125-126 °C) matched that reported for the multiply recrystallised material obtained by the previous route.[9] However, the specific rotation of compound (2) produced by the method described here was much lower {$[\alpha]_D$ = -0.4 *vs* $[\alpha]_D$ = -33} than that reported[9] for material generated using the earlier route. Fortunately a sample of compound (2) derived by the earlier sequence was still available and a re-determination of the specific rotation resulted in a value identical to that observed for the newly prepared sample. Consequently, we believe that our earlier determination[9] of optical rotation for compound (2) to be in error. Given the absence of any racemisation pathways in the synthetic sequence just described as well as the high levels of enantioselectivity obtained in the SAE reaction leading to compound (7) we conclude that phosphine oxide (2) produced by the method described here has been obtained in >95% ee.

Efforts are now underway to exploit compound (2) as a key building block in the total synthesis of herboxidiene.[8] Results will be described in due course.

Experimental

Melting points were recorded with a Kofler hot stage apparatus and are uncorrected. Proton (^1H) and carbon (^{13}C) n.m.r. spectra were recorded with a Varian Gemini 300 spectrometer operating at 300 MHz for proton and 75 MHz for carbon. All such spectra were recorded in deuterochloroform (chloroform-d) solution at 22 °C. The protonicities of the carbon atoms observed in ^{13}C n.m.r. spectra were determined by attached proton test (a.p.t.) experiments. Infrared spectra (υ_{max}) were recorded with either a Perkin-Elmer 983G infrared spectrophotometer or a Perkin-Elmer 1800 Series FTIR spectrophotometer. Unless otherwise specified, samples were analysed as thin liquid films on potassium bromide plates. Low resolution electron-impact mass spectra (*m/z*) were recorded at 70 eV on a VG Micromass 7070F mass spectrometer. High resolution mass spectra were recorded with the same instrument. Unless otherwise stated, optical rotations were measured in spectroscopic grade chloroform at 22 °C using a Perkin-Elmer 241 Polarimeter. Diethyl ether (Et_2O) and tetrahydrofuran (thf) were distilled under nitrogen from sodium benzophenone ketyl. Dichloromethane (CH_2Cl_2), ethyl acetate (EtOAc) and hexane were each distilled from calcium hydride. Ethanol and methanol (CH_3OH) were distilled from their respective magnesium alkoxide salts. Ozonolyses were performed using a Wallace and Tiernan Ozonator with the oxygen flow rate and power set at approximately 25 l/h and 200 V, respectively. Flash chromatographic separations were conducted according to the method of Still *et al.*[18]

Ethyl (E)-*2,6-Heptadienoate (6).*

DMSO (23.7 ml, 334 mmol) was added to a magnetically stirred solution of oxalyl chloride (13.4 ml, 153 mmol) in CH_2Cl_2 (480 ml) maintained under a nitrogen atmosphere at -78 °C. After 0.1 h 4-penten-1-ol (5) (12.0 g, 139 mmol, ex ALDRICH) was added, dropwise, followed, after a further 0.25 h, by triethylamine (134 ml, 961 mmol). The resulting mixture was stirred for 0.5 h at -78 °C then warmed to room temperature and treated with (carbethoxymethylene)triphenylphosphorane[19] (72.8 g, 209 mmol) in dry CH_2Cl_2 (110 ml). After 2 h at 18 °C the reaction mixture was quenched with water (200 ml) and the

separated aqueous layer was extracted with CH_2Cl_2 (3 x 100 ml). The combined organic layers were washed with brine (1 x 75 ml) then dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a light-yellow oil. An ethyl acetate/hexane (1:9 v/v) solution of this material was filtered through a short pad of t.l.c. grade silica gel to afford, after concentration of the filtrate, the title ester (6)[12,20] (21.0 g, 98%) as a light-yellow oil. ν_{max} 3078, 2980, 2933, 1721, 1655, 1446, 1367, 1315, 1266, 1206, 1176, 1044, 989, 914 and 852 cm^{-1}. ^1H n.m.r. δ 6.93 (dt, J = 15.6 and 5.7 Hz, 1H), 5.84-5.73 (complex m, 2H), 5.06-4.96 (complex m, 2H), 4.15 (q, J = 7.1 Hz, 2H), 2.32-2.17 (complex m, 4H), 1.26 (t, J = 7.1 Hz, 3H). ^{13}C n.m.r. δ 166.5 (C), 148.2 (CH), 137.0 (CH), 121.6 (CH), 115.4 (CH_2), 60.1 (CH_2), 32.0 (CH_2), 31.4 (CH_2), 14.2 (CH_3). Mass spectrum *m/z* 154 (6%, $M^{+\cdot}$), 109 [30, $(M - C_2H_5O\cdot)^+$] and 81 [100, $(M - C_2H_5OCO\cdot)^+$]. This material was of sufficient purity for use in the next step of the reaction sequence.

(E)-*2,6-Heptadien-1-ol (4).*

Di-isobutylaluminium hydride (325 ml of a 1.0 M solution in hexane, 325 mmol, ex ALDRICH) was added dropwise (*via* syringe) to a magnetically stirred solution of ethyl (*E*)-2,6-heptadienoate (6) (20.0 g, 130 mmol) in CH_2Cl_2 (650 ml) maintained under a nitrogen atmosphere at -78 °C. The resulting mixture was stirred for 2 h at –78 °C then warmed to 18 °C and quenched with tartaric acid (200 ml of a 1 M aqueous solution). Stirring was continued until two distinct layers were observed (0.25 h). The separated aqueous layer was extracted with CH_2Cl_2 (3 x 200 ml) and the combined organic phases were washed with brine (1 x 200 ml) then dried ($MgSO_4$), filtered and concentrated under reduced pressure. Subjection of the material thus obtained to flash chromatography (silica gel, 1:4 v/v ethyl acetate/hexane elution) and concentration of the appropriate fractions (R_f = 0.25) afforded the title compound (4)[12,21] (12.4 g, 85%) as a light-yellow oil. ν_{max} 3326, 2923, 1641, 1437, 1087, 1000, 970 and 911 cm^{-1}. ^1H n.m.r. δ 5.85-5.65 (complex m, 3H), 5.04-4.94 (complex m, 2H), 4.07 (d, J = 4.4 Hz, 2H), 2.15-2.13 (complex m, 4H) and 1.67 (s, 1H). ^{13}C n.m.r. δ 138.0 (CH), 132.4 (CH), 129.3

(CH), 114.8 (CH_2), 63.7 (CH_2), 33.2 (CH_2) and 31.5 (CH_2). Mass spectrum *m/z* 111 [1%, $(M\text{-}H\cdot)^+$], 94 [13, $(M\text{ -}HO\cdot)^+$] and 79 (100).

*(2*R-trans)*-2,3-Oxiranehept-6-en-1-ol [(+)-(7)].*

SAE of allylic alcohol (4), so as to afford epoxide (+)-(7), was carried out according to the method of Sharpless *et al.*[22] Thus, a magnetically stirred suspension of finely powdered and activated 4 Å molecular sieves (1.0 g) in dry CH_2Cl_2 (137 ml) was cooled to -40 °C then treated, sequentially, with diethyl *D*-(-)-tartrate (0.92 ml, 5.38 mmol), Ti(O-*i*-Pr)$_4$ (1.32 ml, 4.50 mmol) and *tert*-butyl hydroperoxide (17.2 ml of a 5.2 M solution in isooctane, 89 mmol – prepared by extraction of 70% aqueous *tert*-butylhydroperoxide ex ALDRICH[22]). The resulting mixture was stirred at -40 °C for 0.5 h then a solution of compound (4) (5.0 g, 44.6 mmol) in CH_2Cl_2 (20 ml) was added, *via* cannula, at such a rate as to maintain the reaction temperature below -20 °C. After an additional 3 h at -20 °C the reaction mixture was warmed to 0 °C then treated with water (26 ml). The reaction mixture was then warmed to 18 °C and after a further 1 h treated with NaOH (6.0 ml of a 30% aqueous solution saturated with sodium chloride) and stirred vigorously. After *ca.* 0.2 h of stirring, the mixture was filtered through a small pad of Celite™ then the separated aqueous layer was extracted with CH_2Cl_2 (3 x 150 ml). The combined organic layers were dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a light-yellow oil. Subjection of this material to flash chromatography (silica gel, 3:7 v/v ethyl acetate/hexane elution) and concentration of the appropriate fractions (R_f = 0.3) afforded the *title compound (7)* (4.00 g, 70%) as a clear colourless oil, $[\alpha]_D$ = +33 (c 1.2). ν_{max} 3401, 3078, 2979, 2928, 1641, 1449, 1088, 1030, 997, 914, 882 and 642 cm^{-1}. ^1H n.m.r. δ 5.90-5.73 (complex m, 1H), 5.10-4.95 (complex m, 2H), 3.94-3.88 (complex m, 1H), 3.66-3.58 (m, 1H), 3.01-2.90 (complex m, 2H), 2.20 (m, 2H), 1.76 (t, *J* = 6.5 Hz, 1H) and 1.71-1.64 (complex m, 2H); ^{13}C n.m.r. δ 137.4 (CH), 115.3 (CH_2), 61.7 (CH_2), 58.6 (CH), 55.4 (CH), 30.8 (CH_2) and 30.1 (CH_2). Mass spectrum *m/z* 97 [18%, $(M\text{ }-HOCH_2\cdot)^+$] and 67 (100).

(±)-trans-2,3-Oxiranehept-6-en-1-ol [(±)-(7)].

A magnetically stirred solution of allylic alcohol (4) (50 mg, 0.45 mmol) in CH_2Cl_2 (2.5 ml) was treated, portion-wise, with *m*-chloroperbenzoic acid (132 mg of technical grade material containing *ca.* 70% peracid, *ca.* 0.54 mmol). After 2 h the reaction mixture was quenched with $Na_2S_2O_5$ (5 ml of a 1 M aqueous solution). The separated organic phase was washed with $NaHCO_3$ (1 x 5 ml) and water (1 x 5 ml) then dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a light-yellow oil. Subjection of this material to flash chromatography (silica gel, 1:4 v/v ethyl acetate/hexane elution) followed by concentration of the appropriate fractions (R_f = 0.3) then afforded the *title compound (±)-(7)* (25 mg, 44%) as a clear, colourless oil. This material was identical, as judged by ^1H n.m.r., ^{13}C n.m.r., mass spectral and infra-red analysis, with the material obtained using the SAE protocol described above.

Mosher Ester Analysis of Epoxides (+)-(7) and (±)-(7). Formation of Ester (8) and a Diastereoisomer there-of.

A nitrogen atmosphere was established over a magnetically stirred solution of DMAP (18 mg, 0.15 mmol) and triethylamine (0.1 ml) in CH_2Cl_2 (0.5 ml) which was then treated with epoxide (+)-(7) (19.2 mg, 0.15 mmol) and (+)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride[22] (0.04 ml, 0.20 mmol). The resulting solution became warm and turned orange in colour. After 0.1 h the reaction mixture was treated with $NaHCO_3$ (5 ml of a saturated aqueous solution) and extracted with CH_2Cl_2 (2 x 10 ml). The combined organic extracts were washed with brine (1 x 5 ml) then dried ($MgSO_4$), filtered and concentrate under reduced pressure to afford a pale-yellow oil which was subjected to flash chromatography (silica, 1:4 v/v ethyl acetate/hexane elution). Concentration of the appropriate fractions (R_f = 0.4) afforded *Mosher ester (8)* (22 mg, 42%) as a clear, colourless oil. ^1H n.m.r. (C_6D_6) δ 7.82 (d, *J* = 7.6 Hz, 2H), 7.35-7.05 (complex m, 3H), 5.69 (m, 1H), 5.00 (m, 2H), 4.30 (dd, *J* = 12.2 and 3.2 Hz, 1H), 3.80 (dd, *J* = 12.2 and 5.8 Hz, 1H), 3.54 (s, 3H), 2.63 (m, 1H), 2.53 (m, 1H), 1.97 (m, 2H), 1.32 (m, 2H).

The racemic epoxide (±)-(7) (25 mg, 0.20 mmol) was converted into the corresponding mixture of diastereoisomeric Mosher esters by reaction with (+)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride under the conditions described immediately above. ^{1}H n.m.r. analysis of this material revealed it to be a 1:1 mixture of compound (8) and the diastereoisomeric ester derived from *ent*-(7). The most diagnostic ^{1}H n.m.r. signals due to the (*R*)-MTPA ester derivative of *ent*-(7) appear (in C_6D_6) at δ 4.14 (dd, *J* = 12.2 and 3.2 Hz, 1H) and 3.90 (dd, *J* = 12.2 and 5.8 Hz, 1H) [the corresponding signals for (8) appear at δ 4.30 and 3.80 respectively (see preceding paragraph)].

(2S,3S)-3-Methyl-6-heptene-1,2-diol (9).

Trimethylaluminium (131 ml of a 2.0 M solution in hexane, 262 mmol, ex ALDRICH) was added, dropwise, to a magnetically stirred solution of epoxide (7) (11.15 g, 87 mmol) in CH_2Cl_2 (90 ml) maintained at 0 °C under a nitrogen atmosphere. After addition was complete, the reaction mixture was stirred at 18 °C for 10 h and then chilled (0 °C) and quenched (CAUTION) with HCl (75 ml of 1 M aqueous solution). The aqueous layer was extracted with CH_2Cl_2 (3 x 150 ml) and the combined organic layers washed with water (1 x 100 ml) then dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a light-yellow oil. Subjection of this material to flash chromatography (silica gel, 1:1 v/v ethyl acetate/hexane elution) and concentration of the appropriate fractions (R_f = 0.4) afforded the *title compound (9)* (10.4 g, 83%) as a clear, colourless oil, $[\alpha]_D$ = -5.7 (c 1.2) [Found: $(M\text{-}H\cdot)^+$, 143.1070. $C_8H_{16}O_2$ requires $(M\text{-}H\cdot)^+$, 143.1072]. ν_{max} 3368, 3077, 2962, 2928, 1640, 1458, 1380, 1073, 995, 909 and 880 cm^{-1}. ^{1}H n.m.r. δ 5.78 (m, 1H), 5.03-4.88 (complex m, 2H), 3.70-3.60 (complex m, 1H), 3.53-3.40 (complex m, 2H), 3.20 (br s, 2H), 2.20-2.08 (complex m, 1H), 2.05-1.90 (complex m, 1H), 1.70-1.54 (complex m, 2H), 1.29-1.18 (complex m, 1H) and 0.88 (d, *J* = 7.0 Hz, 3H). ^{13}C n.m.r. δ 138.8 (CH), 114.5 (CH_2), 76.1 (CH), 64.6 (CH_2), 35.5 (CH), 31.6 (CH_2), 31.1 (CH_2) and 15.1 (CH_3). Mass spectrum *m/z* 145 [3%, $(M+H)^+$], 144 (3, $M^{+\cdot}$), 143 [2, $(M-H\cdot)^+$], 95 (100) and 71 (53).

(2S, 3S)-3-Methyl-6-heptene-1,2-diol Diacetate (10).

A magnetically stirred solution of diol (9) (5.54 g, 38.5 mmol) in pyridine (21 ml) was treated with acetic anhydride (12.7 ml, 134 mmol) and 4-(*N*,*N*-dimethylamino)pyridine (10 mg, 0.08 mmol). The resulting mixture stirred at 18 °C for 3 h then poured onto ice (*ca.* 50 g) and extracted with ether (1 x 100 ml). The separated organic phase was washed with HCl (2 x 20 ml of a 1 M aqueous solution), $NaHCO_3$ (2 x 20 ml of a saturated aqueous solution) and brine (1 x 20 ml) then dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a light-yellow oil. Subjection of this material to flash chromatography (silica gel, 3:7 v/v ethyl acetate/hexane elution) and concentration of the appropriate fractions (R_f = 0.7) afforded the *title compound (10)* (8.40 g, 96%) as a clear, colourless oil, $[\alpha]_D$ = +5.24 (c 1.3) [Found: $(M+H)^+$, 229.1440. $C_{12}H_{20}O_4$ requires $(M+H)^+$, 229.1440]. ν_{max} 2973, 2937, 1744, 1641, 1458, 1371, 1227, 1048, 1020, 913 and 605 cm^{-1}. ^1H n.m.r. δ 5.76 (m, 1H), 5.03-4.90 (complex m, 3H), 4.27 (dd, J = 12.0 and 3.0 Hz, 1H), 4.05 (dd, J = 12.0 and 4.2 Hz, 1H), 2.15-1.90 (complex m, 2H), 2.06 (s, 3H), 2.03 (s, 3H), 1.85-1.73 (complex m, 1H), 1.50 (m, 1H), 1.23 (m, 1H) and 0.92 (d, J = 6.9 Hz, 3H). ^{13}C n.m.r. δ 170.8 (C), 170.6 (C), 138.2 (CH) 114.8 (CH_2), 74.9 (CH), 63.6 (CH_2), 33.6 (CH), 31.3 (CH_2), 31.0 (CH_2), 21.0 (CH_3), 20.9 (CH_3) and 15.0 (CH_3). Mass spectrum *m/z* 229 [2%, $(M+H)^+$], 213 [24, $(M-H_3C\cdot)^+$], 115 (76), 114 (78), 108 (90), 95 (100), 93 (96) and 79 (70).

[S-(R,R*)]-5,6-bis(Acetyloxy)-4-methylhexenal (11).*

A magnetically stirred solution of diacetate (10) (10.50 g, 45.65 mmol) in CH_2Cl_2 (575 ml) was cooled to -78 °C then treated with a stream of ozone gas until a blue colour persisted. The reaction mixture was then warmed to -30 °C and triphenylphosphine (12.0 g, 45.65 mmol) was carefully added in portions. After the addition was complete, the reaction mixture was allowed to warm to room temperature. The solvent was then removed under reduced pressure and the residue there-by obtained was subjected to flash chromatography (silica gel, 3:7 v/v ethyl acetate/hexane elution). Concentration of the appropriate fractions (R_f = 0.3) gave the title compound (11)[9] (8.40 g, 79%) as a pale-

yellow oil, $[\alpha]_D$ = +7.3 (c 2.0 in MeOH) [Found: $(M+H)^+$, 231.1232. Calcd for $C_{11}H_{18}O_5$ $(M+H)^+$, 231.1232]. ν_{max} 2967, 2727, 1744, 1371, 1227, 1048, 959 and 605 cm^{-1}. ^1H n.m.r. δ 9.77 (s, 1H), 4.94 (m, 1H), 4.31 (dd, *J* = 12.1 and 2.9 Hz, 1H), 4.05 (dd, *J* = 12.1 and 6.8 Hz, 1H), 2.60-2.30 (complex m, 2H), 2.07 (s, 3H), 2.04 (s, 3H), 1.90-1.72 (complex m, 2H), 1.54-1.44 (complex m, 1H) and 0.93 (d, *J* = 6.8 Hz, 3H). ^{13}C n.m.r. δ 201.8 (CH), 170.8 (C), 170.6 (C), 74.5 (CH), 63.4 (CH_2), 41.2 (CH_2), 33.5 (CH), 24.1 (CH_2), 21.0 (CH_3), 20.8 (CH_3) and 15.1 (CH_3); Mass spectrum *m/z* 231 [15%, $(M+H)^+$], 115 (60), 103 (53), 97 (100) and 84 (48).

Methyl {S-[R, R*-(Z)]}-7,8-bis(Acetyloxy)-6-methyl-2-octenoate (12).*

$KN(TMS)_2$ (73.0 ml of a 0.5 M solution in toluene, 36.5 mmol) was added, dropwise, to a magnetically stirred solution of *bis*(2, 2, 2-trifluoroethyl)(methoxycarbonylmethyl)phosphon -ate (7.73 ml, 36.5 mmol) and 18-crown-6/CH_3CN complex[23] (48.3 g, 183 mmol) in dry thf (140 ml) maintained at -78 °C under an atmosphere of nitrogen. The reaction mixture was stirred at -78 °C for 0.5 h then treated with aldehyde (11) (8.4 g, 36.52 mmol). After 1 h at this temperature, the reaction mixture was quenched with NH_4Cl (60 ml of a saturated aqueous solution) then allowed to warm to room temperature. The resulting mixture was extracted with ether (3 x 50 ml) and the combined organic phases were washed with water (1 x 100 ml) then dried ($MgSO_4$), filtered and concentrated under reduced pressure. Subjection of the material thus obtained to flash chromatography (silica gel, 3:7 v/v ethyl acetate/hexane elution) and concentration of the appropriate fractions (R_f = 0.4) afforded the title ester (12)[9] (8.35 g, 80%) as a pale-yellow oil, $[\alpha]_D$ = +9.9 (c 5.4) [Found: $(M+H)^+$, 287.1495. Calcd for $C_{14}H_{22}O_6$ $(M+H)^+$, 287.1495]. ν_{max} 2953, 1743, 1645, 1439, 1371, 1226, 1176, 1048 and 821 cm^{-1}. ^1H n.m.r. δ 6.18 (m, 1H), 5.78 (br. d, *J* = 11.5 Hz, 1H), 4.95 (td, *J* = 6.8 and 2.9 Hz, 1H), 4.29 (dd, *J* = 12.0 and 2.9 Hz, 1H), 4.06 (dd, *J* = 12.0 and 7.1 Hz, 1H), 3.70 (s, 3H), 2.68 (m, 2H), 2.07 (s, 3H), 2.04 (s, 3H), 1.82 (m, 1H), 1.65-1.50 (complex m, 1H), 1.35-1.20 (complex m, 1H) and 0.96 (d, *J* = 7.0 Hz, 3H). ^{13}C n.m.r. δ 170.8 (C), 170.6 (C), 166.7 (C), 149.8 (CH), 119.7 (CH), 74.9 (CH_3), 63.5

(CH_2), 51.0 (CH), 33.9 (CH), 31.3 (CH_2), 26.3 (CH_2), 21.0 (CH_3), 20.8 (CH_3) and 15.0 (CH_3). Mass spectrum *m/z* 287 [5%, $(M+H)^+$], 166 (52), 153 (70), 139 (100), 107 (74) and 81 (90).

Methyl [2R-(2α,5β,6α)]-Tetrahydro-6-(hydroxymethyl)-5-methyl-2H-pyran-2-acetate (13).

A mixture of ester (12) (8.35 g, 29.20 mmol), K_2CO_3 (20.2 g, 146 mmol) and methanol (42 ml) was stirred at 18 °C for 24 h then filtered through a sintered glass funnel. Water (100 ml) was added to the filtrate which was acidified to pH 2-3 with HCl (concentrated aqueous solution). The resulting mixture was extracted with diethyl ether (3 x 50 ml) and the combined extracts dried ($MgSO_4$), filtered and then concentrated under reduced pressure. The light-yellow oil obtained in this manner was suspended in methanol (50 ml) containing H_2SO_4 (six drops of 98% acid) and the resulting mixture stirred at 18 °C for 16 h then poured onto ice (50 g) and extracted with diethyl ether (3 x 50 ml). The combined organic extracts were washed with $NaHCO_3$ (1 x 50 ml of a saturated aqueous solution) then dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford a light-yellow oil. Subjection of this material to flash chromatography (silica gel, 3:7 v/v ethyl acetate/hexane elution) and concentration of the appropriate fractions (R_f = 0.25) afforded the title compound (13)[9] (4.18 g, 71%) as a clear colourless oil, $[\alpha]_D$ = +9.8 (c 1.0) {lit.[2] $[\alpha]_D$ = +9.4} [Found: $(M-H_2O)^{+\cdot}$, 184.1097. Calcd for $C_{10}H_{18}O_4$ ($M-H_2O)^{+\cdot}$, 184.1099). ν_{max} 3458, 2928, 2873, 1738, 1437, 1199, 1087 and 1019 cm^{-1}. ^1H n.m.r. δ 3.80-3.63 (complex m, 2H), 3.65 (s, 3H), 3.47 (ddd, *J* = 11.4, 7.1 and 4.3 Hz, 1H), 3.10 (ddd, *J* = 9.8, 7.1 and 2.7 Hz, 1H), 2.53 (dd, *J* = 15.2 and 7.7 Hz, 1H), 2.40 (dd, *J* = 15.2 and 5.4 Hz, 1H), 2.21 (dd, *J* = 8.2 and 4.4 Hz, 1H), 1.80-1.72 (complex m, 1H), 1.70-1.60 (complex m, 1H), 1.48-1.12 (complex m, 3H), and 0.80 (d, *J* = 6.5 Hz, 3H). ^{13}C n.m.r. δ 171.6 (C), 83.5 (CH), 74.0 (CH), 63.7 (CH_2), 51.6 (CH_3), 41.1 (CH_2), 32.1 (CH_2), 31.5 (CH_2), 31.1 (CH) and 17.1 (CH_3). Mass spectrum *m/z* 203 [26%, $(M+H)^+$], 171 [100, $(M-H_3CO\cdot)^+$], 139 (73), 129 (57) and 97 (54).

Methyl [2R-(2α,5β,6α)]-6-Formyltetrahydro-5-methyl-2H-pyran-2-acetate (14). A solution of alcohol (13) (1.0 g, 4.95 mol) and triethylamine (4.5 ml, 32.1 mmol) in CH_2Cl_2 (14.2 ml) was added, dropwise, to a magnetically stirred solution of sulfur trioxide/pyridine complex (2.52 g, 15.8 mmol, ex ALDRCH) in DMSO/CH_2Cl_2 (15.6 ml of a 3:2 v/v mixture) maintained at 0 °C (ice-bath) under a nitrogen atmosphere. The reaction mixture was warmed to 18 °C and after stirring for a further 1 h it was treated with water (130 ml) then extracted with hexane (3 x 75 ml). The combined organic phases were washed with brine (1 x 50 ml) then dried ($MgSO_4$), filtered and concentrated under reduced pressure. The light-yellow oil thus obtained was subjected to flash chromatography (silica gel, 3:7 v/v ethyl acetate/hexane elution) and concentration of the appropriate fractions (R_f = 0.4) then afforded the title compound (14)[9] (594 mg, 60%) as a clear colourless oil, $[\alpha]_D$ = -65 (c 0.45) {lit.[2] $[\alpha]_D$ = –62 (c 0.5 in $CHCl_3$)} [Found: (M –CHO·)$^+$, 171.1020. Calcd for $C_{10}H_{16}O_4$ (M –CHO·)$^+$, 171.1021). ν_{max} 2932, 1740, 1437, 1200, 1090, 1021 and 857 cm^{-1}. ^{1}H n.m.r. δ 9.51 (d, *J* = 2.3 Hz, 1H), 3.80 (m, 1H), 3.67 (s, 3H), 3.41 (dd, *J* = 10.6 and 2.3 Hz, 1H), 2.61 (dd, *J* = 15.4 and 7.6 Hz, 1H), 2.44 (dd, *J* = 15.4 and 5.4 Hz, 1H), 1.88 (m, 1H), 1.70 (m, 1H), 1.64-1.50 (complex m, 1H), 1.45-1.20 (complex m, 2H), 0.91 (d, *J* = 6.6 Hz, 3H). ^{13}C n.m.r. δ 200.6 (CH), 171.4 (C), 86.7 (CH), 73.5 (CH), 51.7 (CH_3), 41.0 (CH_2), 32.1 (CH_2), 30.8 (CH_2), 30.5 (CH) and 16.3 (CH_3). Mass spectrum *m/z* 201 [14%, (M+H)$^+$], 171 [100, (M –CHO·)$^+$], 139 (88), 127 (52), 111 (57), 97 (88), 81 (57) and 69 (59).

Methyl [2R-(2α,5β,6α)]-6-Acetyltetrahydro-5-methyl-2H-pyran-2-acetate (15). Methylmagnesium chloride (0.83 ml of a 3 M solution in thf, 2.5 mmol) was added, dropwise, to a magnetically stirred solution of aldehyde (14) (500 mg, 2.5 mmol) in thf (12.5 ml) maintained at -78 °C under a nitrogen atmosphere. After addition was complete the reaction mixture was allowed to warm to 0 °C then stirred at this temperature for a further 1 h then poured onto a mixture of ice (*ca.* 20 g) and NH_4Cl (20 ml of a saturated aqueous solution). The resulting mixture was extracted with ether (3 x 20 ml) and the combined organic phases washed with water (1 x 30 ml) then dried ($MgSO_4$), filtered and

concentrated under reduced pressure to afford a light-yellow oil (190 mg). Subjection of this material to flash chromatography (silica gel, 3:7 v/v ethyl acetate/hexane elution) and concentration of the appropriate fractions (R_f = 0.3) afforded the expected mixture of diastereoisomeric 2°-alcohols as a clear, colourless oil. This material was dissolved in CH_2Cl_2 (8.0 ml) and the resulting solution treated with the Dess-Martin periodinane[17] (560 mg, 1.32 mmol). The mixture thus obtained was stirred at 18 °C for 1 h then diluted, successively, with diethyl ether (10 ml), $NaHCO_3$ (5 ml of a saturated aqueous solution) and $Na_2S_2O_3$ (5 ml of a 1 M aqueous solution). Stirring was continued until two layers became apparent. The separated aqueous phase was extracted with diethyl ether (3 x 10 ml) and the combined organic phases were washed with brine (1 x 10 ml) then dried ($MgSO_4$), filtered and concentrated under reduced pressure. The resulting light-yellow oil was subjected to flash chromatography (silica gel, 3:7 v/v ethyl acetate/hexane elution) and concentration of the appropriate fractions (R_f = 0.3) then afforded the title compound (15)[9] (90 mg, 17%) as a clear colourless oil $[\alpha]_D$ = -91 (c 1.2) {lit.[2] $[\alpha]_D$ = –95 (c 1.5 in $CHCl_3$)} [Found: $(M+H)^+$, 215.1282. Calcd for $C_{11}H_{18}O_4$ $(M+H)^+$, 215.1283]. ν_{max} 2931, 1741, 1719, 1437, 1354, 1199, 1083, 1022 and 894 cm^{-1}. ^1H n.m.r. δ 3.78 (m, 1H), 3.67 (s, 3H), 3.41 (d, J = 10.2 Hz, 1H), 2.57 (dd, J = 15.1 and 7.6 Hz, 1H), 2.44 (dd, J = 15.1 and 5.4 Hz, 1H), 2.14 (s, 3H), 1.87 (m, 1H), 1.72-1.67 (complex m, 1H), 1.60-1.18 (complex m, 3H) and 0.82 (d, J = 6.6 Hz, 3H). ^{13}C n.m.r. δ 207.9 (C), 171.5 (C), 89.0 (CH), 73.7 (CH), 51.7 (CH_3), 41.1 (CH_2), 32.2 (CH_2), 31.8 (CH_3), 31.1 (CH_2), 25.8 (CH) and 16.9 (CH_3). Mass spectrum *m/z* 215 [5%, $(M+H)^+$], 171 [100, $(M -CH_3CO\cdot)^+$], 139 (95), 111 (61) and 97 (92).

Methyl {2R-[2α,5β,6α(E)}-6-(3-Bromo-1-methyl-1-propenyl)tetrahydro-5-methyl-2H-pyran-2-acetate (16).

Vinylmagnesium bromide (1.6 ml of a 1 M solution in thf, 1.58 mmol, ex ALDRICH) was added, dropwise, to a magnetically stirred solution of ketone (15) (339 mg, 1.58 mmol) in thf (65 ml) maintained at -78 °C under a nitrogen atmosphere. The resulting mixture was stirred at -78 °C for a further 1 h then warmed to 0 °C, poured into NH_4Cl (25 ml of a

saturated aqueous solution) and extracted with diethyl ether (3 x 50 ml). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a light-yellow oil (203 mg) which was subjected to flash chromatography (silica gel, 1:4 v/v ethyl acetate/hexane elution). Concentration of the appropriate fractions (R_f = 0.3) then afforded the expected vinyl alcohol which was immediately subjected to the brominative rearrangement reaction. Thus, PBr_3 (50 µl, 0.5 mmol) was injected, *via* syringe, into a magnetically stirred solution of the vinyl alcohol (100 mg, 0.41 mmol) in diethyl ether (10 ml) maintained at 0 °C under a nitrogen atmosphere. After the addition was complete, the reaction mixture was stirred at 0 °C for a further 1 h and then poured onto ice (*ca.* 10 g). The resulting mixture was extracted with diethyl ether (1 x 30 ml) and the separated organic phase dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a light-yellow oil. Subjection of this material to flash chromatography (silica gel, 1:4 v/v ethyl acetate/hexane elution) afforded, after concentration of the appropriate fractions (R_f = 0.3), the title bromide (16)[9] (117 mg, 93%) as a clear, colourless oil, $[\alpha]_D$ = -29 (c 2.1) {lit.[9] $[\alpha]_D$ = –5.2 (c 1.5 in $CHCl_3$)} [Found: (M –Br·)$^+$, 225.1495. Calcd for $C_{13}H_{21}BrO_3$ requires (M –Br·)$^+$, 225.1491]. ν_{max} 2951, 2926, 1740, 1436, 1200, 1069, 1019 and 865 cm-1. ^{1}H n.m.r. δ 5.69 (t, *J* = 9.0 Hz, 1H), 4.00 (m, 2H), 3.80-3.70 (complex m, 1H), 3.66 (s, 3H), 3.35 (d, *J* = 9.8 Hz, 1H), 2.58 (dd, *J* = 15.2 and 6.5 Hz, 1H), 2.40 (dd, *J* = 15.2 and 6.5 Hz, 1H), 1.90-1.80 (complex m, 1H), 1.69 (s, 3H), 1.70-1.65 (complex m, 1H), 1.62-1.47 (complex m, 1H), 1.40-1.15 (complex m, 2H) and 0.71 (d, *J* = 6.7 Hz, 3H). ^{13}C n.m.r. δ 171.7 (C), 141.5 (C), 123.9 (CH), 89.5 (CH), 73.8 (CH), 51.6 (CH_3), 41.2 (CH_2), 32.3 (CH), 32.2 (CH_2), 31.5 (CH_2), 28.2 (CH_2), 17.4 (CH_3), 11.5 (CH_3). Mass spectrum *m/z* 224 [8%, (M -Br·)$^+$] and 121 (100).

*Methyl {2*R*-[2α,5β,6α(*E*)}-6-[3-(diphenylphosphinoyl)-1-methyl-1-propenyl]tetrahydro-5-methyl-2*H*-pyran-2-acetate (2).*

A magnetically stirred solution of bromide (16) (100 mg, 0.33 mmol) and diphenylethoxyphosphine (143 µl, 0.66 mmol, ex ALDRICH) in thf (10 ml) was heated at

reflux until the starting materials had been consumed (*ca.* 2 h). The cooled reaction mixture was concentrated under reduced pressure and the resulting solid recrystallised (diethyl ether) to give the phosphine oxide (2)[9] (119 mg, 85%) as a fine white powder, m.p. = 125-126 °C (lit.[9] m.p. = 125-126 °C), $[\alpha]_D$ = -0.4 (c 1.4) {lit.[9] $[\alpha]_D$ –32.8 (c 0.5 in $CHCl_3$) – see text} (Found: $M^{+\cdot}$, 426.1962. Calcd for $C_{25}H_{31}O_4P$ requires $M^{+\cdot}$, 426.1960). ν_{max} (KBr disc) 2924, 2847, 1736, 1437, 1180, 1120, 1069, 1018, 745, 719, 697, 555 and 512 cm^{-1}. ^1H n.m.r. δ 7.74 (m, 4H), 7.50 (m, 6H). 5.50 (m, 1H), 3.72-3.60 (complex m, 1H), 3.63 (s, 3H), 3.26 (d, *J* = 9.7 Hz, 1H), 3.23-3.10 (complex m, 2H), 2.54 (dd, *J* = 15.1 and 6.5 Hz, 1H), 2.37 (dd, *J* = 15.1 and 6.4 Hz, 1H), 1.80-1.55 (complex m, 2H), 1.47 (s, 3H), 1.45-1.10 (complex m, 3H) and 0.42 (d, *J* = 6.6 Hz, 3H). ^{13}C n.m.r. δ 171.7 (C), 140.0 (d, C), 133.2 (d, C), 131.9 (CH), 131.0 (d, CH), 128.5 (d, CH), 116.9 (d, CH), 90.0 (CH), 73.8 (CH), 51.5 (CH_3), 41.3 (CH_2), 32.1 (CH_2), 32.0 (CH_3), 31.5 (CH_2), 30.7 (d, CH_2), 17.2 (CH), 12.2 (CH_3) [d = doublet due to ^{13}C-^{31}P coupling]. ^{31}P n.m.r. δ 31.0. Mass spectrum *m/z* 426 (51%, $M^{+\cdot}$), 202 [100, $(Ph_2POH)^{+\cdot}$] and 201 [94, $(Ph_2PO)^+$].

Acknowledgments

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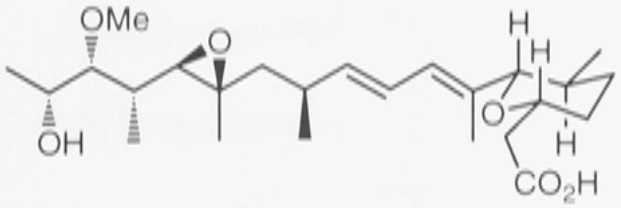

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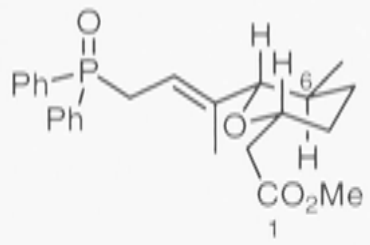

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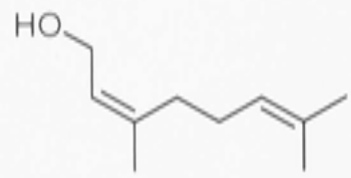

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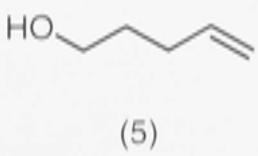
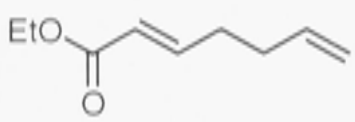


(5)

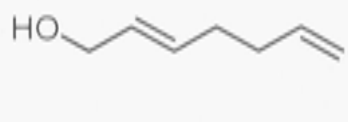
(i) Swern oxidation

(ii) $Ph_3P=C(H)CO_2Et$



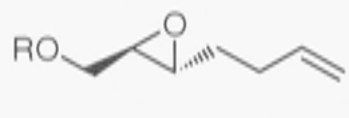
(6)

DIBAL-H



(4)

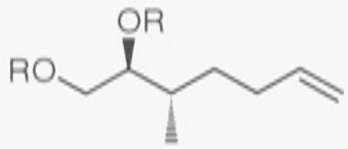
SAE | diethyl (-)-tartrate



Mosher esterification → (7) R=H; (8) R=(*R*)-MTPA

Me_3Al

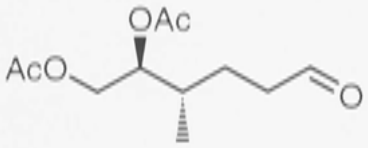
compound (7)



Ac_2O, DMAP, pyridine → (9) R=H; (10) R=Ac

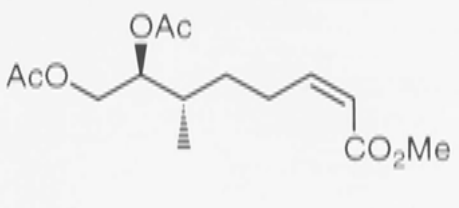
O_3, Ph_3P

compound (10)



(11)

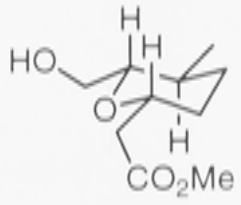
Still-Gennari olefination



(12)

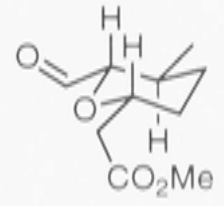
(i) K_2CO_3, MeOH

(ii) MeOH, H_2SO_4



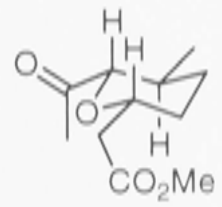
(13)

Parikh-Doering oxidation



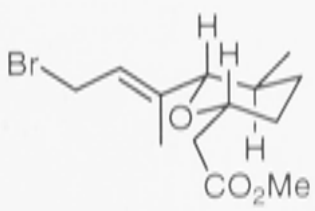
(14)

(i) MeMgCl
(ii) Dess-Martin oxidation



(15)

(i) $H_2C=C(H)MgBr$
(ii) PBr_3



(16)

Ph_2POEt

(2)

Scheme 1